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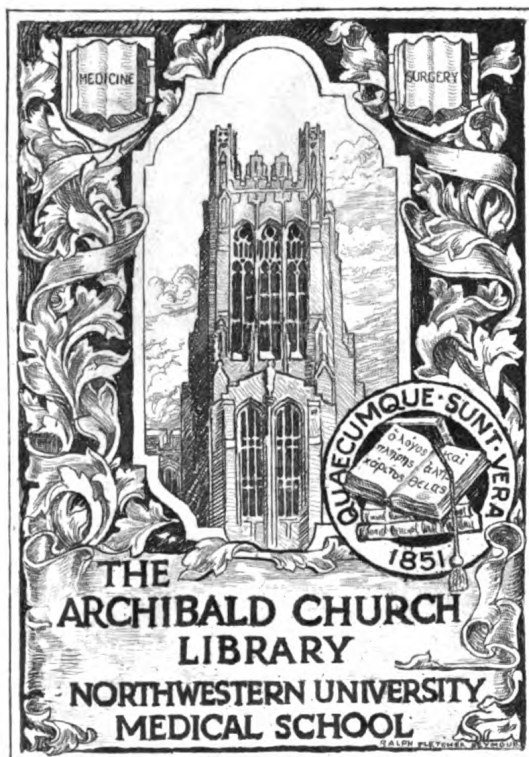
ARCHIVES OF NEUROLOGY  
AND PSYCHIATRY

THE PATHOLOGICAL LABORATORY

LONDON COUNTY ASYLUMS  
CLAYBURY ESSEX

VOL. IV.

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# ARCHIVES OF NEUROLOGY AND PSYCHIATRY

*(With Introductory Paper by Dr. Henry Maudsley).*

FROM THE  
PATHOLOGICAL LABORATORY  
OF THE  
LONDON COUNTY ASYLUMS,  
CLAYBURY, ESSEX.

EDITED BY

FREDERICK WALKER MOTT, M.D., F.R.S., F.R.C.P.,

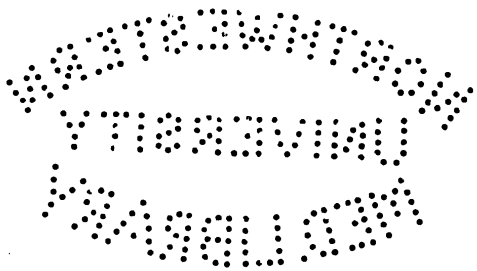
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## PREFACE.

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IN the preface of volume III. of the Archives of Neurology I ventured to express a hope that the London County Council at some future date would establish in London an acute hospital for the investigation and treatment of curable mental cases. I also pointed out that with the establishment of such a hospital a psychiatric clinic might be looked for, on the basis of the Munich institution with its associated laboratories for clinical and pathological research. The Asylums Committee has long been in sympathy with the removal of the Pathological Laboratory to a more central situation, whereby it could be utilized not only by all the officers in the service if they so desired, but also by students and medical practitioners interested in the study of brain diseases. The present laboratory, although admirably equipped, is so far distant that it is not available to the majority of the officers and students interested in the study of the pathology of mental diseases. Economic reasons doubtless prevented the Council from giving effect to a recommendation of the Pathological Sub-Committee of the desirability of removing the laboratory to London. The London County Council having accepted the munificent donation of Dr. Henry Maudsley, there is every reason to hope that a hospital for the treatment and study of acute mental diseases with a psychiatric clinic and associated pathological and clinical laboratories will now be established in London.

In that same preface I further stated that if suitable post-graduate training in medico-psychology and neuro-pathology were established, doubtless the Universities and licensing bodies might be induced to grant a diploma very much on the lines of the Diploma of Public Health which has so largely contributed to raise the science of Public Health to the high position it now holds, thus conferring an inestimable benefit on the nation.

The object, scope, and utility of a hospital in London for acute mental diseases are admirably set forth by Dr. Maudsley himself in his valuable introduction to this volume, and I am quite sure that it will be of inestimable value to all who are interested in the progress of the science of psychiatry, for it lays down the broad principles of research and the necessity of co-operation of certain branches of science which are requisite for the successful investigation of such a complex subject as Mind and its various disorders. The advice of a distinguished alienist physician

of long and extensive experience whose writings and teaching on the pathology of mind have been so lucid and luminous, and who has given also such practical support to research, cannot fail to further stimulate the officers of the London County Asylums and all who are interested in the progress of our knowledge of mental diseases, and I am sure I am voicing the opinion of the Asylums Committee in expressing gratitude for this valuable contribution to the volume; and in view of indications that in the future medical officers in the service will be more ready to contribute scientific papers bearing upon the causation, treatment, and pathology of insanity, I have considered the advisability of making an addition to the title, and it will henceforth bear the name, "Archives of Neurology and Psychiatry." It is hoped and expected that a sufficient number of papers will be forthcoming to keep up its annual publication.

In this volume there are two communications from distinguished foreigners; in neither case has the work been done in the Pathological Laboratory at Claybury, but there are good reasons that these valuable papers should appear in the Archives. The paper that Dr. Ariëns Kappers, Director of the Neurological Institute, Amsterdam, has contributed on "The Phylogenesis of the Palæo-Cortex and Archi-Cortex compared with the Evolution of the Visual Neo-Cortex" was voluntarily offered by this distinguished neurologist for the reason that his researches on the evolution of the smell area in vertebrates corresponded with my researches (published in the last volume) on the evolution of the visual area in mammals. He therefore considered the Archives a very suitable place for this publication. Again, Dr. Giacomo Pighini, of Reggio Emilia, having heard of the researches which have been carried on by Dr. Waldemar Koch and my assistant, Mr. Sydney Mann, upon "The Chemical Study of the Brain in Healthy and Diseased Conditions, with especial reference to Dementia Præcox," offered a paper on "The Organic Metabolism in Dementia Præcox," which in a measure supports some of the conclusions arrived at from the work carried on in this laboratory.

The papers published in this volume do not represent nearly all the work which has been carried on in the laboratory. Three papers have been read at the Royal Society and have been published in the Proceedings, but as they had no direct bearing upon mental diseases and a selection for this volume had to be made, it was thought better to circulate reprints of these and of some other papers—*e.g.*, Dr. Schuster's valuable paper on the examination of three Chinese brains, published in the Journal of Anatomy and Physiology, and several recent communications to the Royal Society of Medicine, in particular one by Dr. Rondoni "On Some Hereditary Syphilitic Affections of the Nervous System."



In conclusion, I wish to thank my assistant, Dr. Candler, for the great help which he has afforded me in carrying out the researches on syphilis and tuberculosis, and for the careful investigations he has made relating to general paralysis and its causation.

My assistant, Mr. Mann, has given me invaluable assistance in preparing this volume for the press and in the preparation of the statistics on tuberculosis. All the microscopic preparations and photo-micrographs have been made by my assistant, Mr. Geary, and to him I am indebted for his valuable help.

FRED<sup>K</sup>. W. MOTT.



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"A MENTAL HOSPITAL.—ITS AIMS AND USES."

By HENRY MAUDSLEY, M.D.

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For a great while the study of mental functions was divided between three kinds of inquirers who, going their separate ways, never imagined that their studies were anywise related. The metaphysical psychologist peered into the recesses of his own mind with the zeal and sense of superiority which have always distinguished him, and with the result for the most part of saying the same thing over and over again, although in sometimes different language; the physiologist pursued his patient researches into the structure and functions of the brain and nervous system without the least regard to the mental functions which they subserve; and the student of mental disorders, wholly concerned with them, dreamed not of bringing the lessons of mental pathology to bear upon the problems of normal psychology. Three classes of persons worked diligently to elucidate the same subject without ever a word to say to each other!

Things have changed and are steadily changing now. Although the metaphysician still takes his lofty flights in regions of transcendental thought, regardless of the concrete which alone gives vital meaning to the abstract, the positive psychologist begins to take perfunctory account of the facts of mental physiology and of the experimental results of psycho-physical investigation. But with small profit hitherto, because, lacking the vital appreciation of them which a thorough anatomical and physiological training can alone give, he appropriates partially and superficially, without assimilating vitally, a few facts which he vitiates, if not eviscerates, by translation into the terms of his traditional vocabulary. For the most part he fails to realise what organic life is and what

a vital organisation signifies, and expects a successful exposition of life in mind, and of mind in life, without a fundamental knowledge of life. Psychology is expected to blossom as the crowning development of biology without the least regard to biology.

Although mind is a word in familiar use the usual conception of it is nowise clear and distinct, nor the use of the word constant and definite. Whatever it be in its essence—even if an incorporeal entity working through corporeal organs—mind in its every function implies a complex organisation of the supreme cerebral centres, a definite mental organisation there, which it does not precede and form, but is informed by, depends upon, and is the function of. Such as it is now it never could have been but for the progressive development of cerebral structure through the ages of animal evolution on earth. If the distinct conception of an exquisitely delicate and complex organisation of finest nervous structure in definite patterns or plexuses, intimately associated, be grasped and held fast, it becomes easier to realise the manner of its disorganisation when its mechanism is damaged, or falls out of gear, or wears out by natural decay; all which effects are constantly happening in the universal flux of things. Substitute the definite notion of a mental organisation for the indefinite notion of mind when thinking and speaking of it, and thought becomes less obscure and confused, more clear and distinct, more positively scientific. As in truth would all thought when men think, or think they think, were they at the pains to substitute mentally the exact definition for the vague word.

Life being a process of conflict and communion between the organism and the external world in the endeavour to maintain a stable equilibrium of growing being to its environment—a succession of transitory equilibriums of elements and of the whole between opposing forces—it is obvious that when the equilibrium between a person and his circumstances is so upset as to issue in a mental derangement two factors co-operate, namely, the innate constitutional strength of the mental organisation and the circumstances of the stress to which it is exposed. When the internal factor is weak, circumstances do such hurt as they could not do to a sound and strong nature, which on its part steadily and successfully encounters all strains and stresses, itself strengthened structurally by the contest and the conquest. Some well-built minds we may be sure that all calamities rudest shocks could not confound. When the disease befalls which is madness the infirmity within conspires with the hostile action without.

Of the two factors the internal, which is a basic inheritance from the family stock, is the most important. Appreciating the share which bacterial toxins and morbid ferments have in the causation of insanity,



it is still right not to underrate the fundamental value of the individual constitution. The delirium of typhoid fever, pneumonia, or other acute disease is not due to the height of the bodily temperature; one person is delirious with a low temperature while another with a high temperature is not delirious; it is due to a native weakness of his mental organisation which search into his ancestral lineage may explain. So, likewise, when a small dose of alcohol easily intoxicates one person, or a larger dose causes an attack of transitory mania instead of an ordinary intoxication, the result is due to an inherited instability of mental organisation; when it is not due, as it may be, to a brain that has been accidentally hurt by a fracture or other injury to the skull rendering the person thenceforth extremely irritable and prone to outbursts of such passionate fury as to be temporary madness. In its elements as in the whole organism to be weak is to invite and suffer hurt.

Surrounded by thousands of hostile agencies—open and secret, mighty and minute—the organism keeps itself in health and strength by virtue of its native strength of vital resistance, possessing which in full measure it triumphantly defies the perilous bacterium and other dangers and adversities of its mortal life. When therefore one mind succumbs to hostile influences which another successfully withstands, the reaction which it makes to its surroundings is not fitly regulated motion along orderly lines of adaptive function but disorderly motion of disintegration. Between the worst and the best minds there are innumerable differences of strength to withstand and of frailty to succumb to hostile attack. A strange theory it was, albeit supported by no less distinguished a philosopher than Locke, that all persons were born with equal mental capacities, the differences of development being due to education. Minds, like bodies, are born constitutionally different; and as nobody is born perfect, everybody presumably has his weak organ, the spot of less resistance in him, which suffers first and most when overstrained or otherwise hurt. The misfortune is when that organ is the brain.

Gross defects or deformities of cerebral structure are visible enough in some cases of idiocy and imbecility. Short of such gross defects, however, there are minute and subtle defects not even microscopically visible or yet otherwise detectable by sense, however powerful its artificial aids. These invisible defects are presumably of two kinds, namely, material disintegration and federal dissociation; the former a positive deterioration or destruction of nervous elements, the latter a disunion of organised parts which ought to act together in integrate union. When the nervous element itself from some cause or other lacks vital force and easily succumbs to overstrain or toxic agencies the damage is positively material, just as it is when motor function is enfeebled or paralysed by

injury to motor nerve centres. When, however, the organisation of federal parts which ought to act together in associated function is impaired the result is dissociated and almost independent action, not otherwise than as when associated movements are dissociated in spasms or convulsions. In the performance of ideas as in the performance of movements ataxic disorder sometimes occurs, a mental not unlike a motor ataxia.

Accordingly the varieties of insanity fall naturally into two principal classes. When the material element is damaged either by direct injury or by toxins introduced into the body, or engendered in it by some mishap in the processes of metabolism, its disordered energies are displayed in the utter incoherencies of delirium and acute delirious mania. Remembering in what furious fashion the virulent bacilli of tetanus and hydrophobia act perniciously on the parts of the nervous system which select them or they select, and thereupon imagining a toxin to select and affect the supreme cerebral centres with a like virulent energy, it is not difficult to conceive the production of an acute delirious insanity. There is then no system or method in the madness, no organisation of disorder, at any rate during the acute stage, albeit more or less coherent organisations of disorder take place when things become chronic. Could we dive into the turbid recesses of the acutely melancholic mind and realise what goes on there we should discover a condition of things in which the formal apprehensions of outward impressions are dissolved and they grossly misinterpreted in consequence; sights, sounds, touch, and odour being translated into threats, signs, omens of hurt. It is strange to see how completely the sufferer then misinterprets innocent words and gestures, seeing in them hidden symbols of danger, mistakes the identities of familiar persons about him, fights against tendered help as if it were a deadly assault. His relations are not with the external world of realities, they are with the illusions into which these are translated by his disordered mental activities. Like as every sane person does sanely, so he creates his own external world, a world of turbulent turmoil, insanely. Low vitality of nerve element is naturally and necessarily accompanied by low spirits; its gravely menaced life, then unable to receive and react fitly, reacts convulsively at random.

In the other class of cases the forms of thought are not entirely disintegrated; the disorder showing itself rather in a dissociation of the federal tracts or centres and in the steady organisation of disorder—in an organised insanity. For instance, the victim of a mania of persecution, rational in other respects, believes himself to be subject to all sorts of impossible persecutions in all sorts of impossible ways, and cannot be brought to doubt the evidence of his own consciousness by the concurrent

and consistent testimony of all those who come in contact with him. In the further development of his mental disorder, vexed and perplexed to account for so strange and persistent a hostility, which he has nowise deserved, he grows into the settled conviction that he is not the person he has hitherto been thought and thought himself to be, but really a person of distinguished, perhaps royal, parentage kept out of his natural rights by a secret conspiracy. Such an amazing system of a so powerfully organised and all-pervading a persecution must have an extraordinary meaning. Given the truth of his premises what other or otherlike conclusion could reason come to? When all is said, reason is always an inevitable machine-like deduction from the premises, which can never be exactly the same in different persons, and at best for a finite being in an infinite universe must necessarily always be incomplete and arbitrary. Take, again, the victim of a jealous and unreasonable suspicion of his wife's secret infidelity who, constantly on the watch indoors and out-of-doors, through windows and keyholes, to discover proofs of her unchaste misdeeds, finds it in the most trivial and perfectly innocent circumstances, translating them into the terms of his dominant mood. He, too, a rational man for the most part in all other respects, all the while perhaps doing fairly his daily work in his business. Side by side in his mind, if not in amity at any rate without open hostility, dwell sound reason and utter unreason; the insane delusion apparently no alien but quite at home there. As in truth it well may be seeing that it is then probably ingraft in the stock and marks an insane inheritance.

In such cases, the normal unions of federal tracts being disjointed, a pathological organisation of disordered activity takes effect. Thus it is that a class of organised insanities differ in symptoms, pathology and mode of causation from the insanities of positive nervous deterioration. In them the question is not so much a question of material injury to nerve element as of morbid growth—of the steady development of a morbid character from the root of a bad constitutional inheritance: an extreme instance indeed of the bad mental growth by which narrow and fixed prejudice blinds the ill-constructed mind to truth, be it never so plain. Nursed passion or prejudice ripens into bad habit of thinking and feeling, and bad habit grows into organised disorder. As in dreams temporarily, so in insanities, organisation of disorder is a constant and natural process. Part of the work in a well-organised mental hospital might not unfitly be a systematic instruction in mental hygiene in its widest sense; instruction based positively on demonstration by actual examples of the natural and necessary effects of bad habits of thought and feeling.

As there are two different classes of insanity so there are two different orders of inquiry: First, a pathological inquiry is concerned with the

minute investigation of the physical and chemical causes of the derangement and with the morbid changes of structure; for which purpose a well-equipped pathological laboratory in the hospital is indispensable. Secondly, a more general inquiry ought to be made into the individual character, the hereditary influences which have wrought in its constitution, the sort of education which it has undergone, and the circumstances of life which have affected its development. These effects are more or less legible in the mental complexion of everybody had we only the insight to discern them; for as the various features of a countenance are woven together in its whole complexion or physiognomy, so the moods of feeling and habits of thought are represented in the individual's mental complexion and declare his character. However that be, the problems of a positive scientific study concern the material constituting the mental fabric and the physico-chemical causes of hurt to it, on the one hand; and, on the other hand, the character of the fabric and its edification.

The latter inquiry is not only a legitimate part of a scientific study of mental pathology, it has also important practical bearings. Obviously it is not sufficient to consider the organism only as a physiological machine liable to be deranged by subtle toxic matters; it is incumbent to study the individual also as a social being. Mental organisation being effected by progressive adaptation to the social as well as the physical environment, tradition, custom and convention constitute a social medium which is ingraft in the individual's nature and to which he must conform outwardly if he is to live and function as a social unit in it. Broadly speaking, insanity is such derangement of mind as prevents its victim from discharging his normal functions in the social body of which he is a member; therefore the nature of the social medium and his relations to it must always be well considered in a true exposition of its causation and character. The feelings, thought and conduct befitting one society or even one station of life in the same society are notoriously quite unsuitable to a different society or to another station in life; so alien from it indeed as to alienate the individual and thus to be a mental alienation. Were a Prime Minister or an Archbishop to do openly in the public street what a savage does indifferently among his huts, or to go about town in his shirt sleeves with a short pipe in his mouth, he would be pretty sure to be counted a person of unsound mind and a proper person to be put under care and treatment. Or were anybody, like an inspired Mahdi, to go about the city proclaiming the immediate end of the world and urging everybody to go down on his knees in instant prayer he would no doubt be sent to a lunatic asylum. So essentially does the special social medium enter into the constitution of the individual mental structure, and so necessary is it to take strict account of the

character of both and their relations in deciding what is and what is not insanity; and that especially when it is a serious question of medical certificates and legal restraint.

Alike in the interests of medical men who certify and are liable to an action at law for what they do, and of those who are liable to be certified and may afterwards be socially prejudiced thereby, it is evidently most desirable that medical students should be taught carefully what is a good and sufficient certificate of insanity, what certification involves, and in what cases it is justified. At present it would hardly be an exaggeration to say that more than half the certificates signed are sent back by the superintendents of asylums for correction or amendment. A well-staffed mental hospital will supply effective means of clinical instruction to students fitting them for their work when they go into medical practice; it will also supply a succession of trained medical men, interested in the special study and imbued with a scientific spirit, available to take office in the county asylums.

Many interesting and important questions, it is needless to say, still await the satisfactory answers which systematic study of insanity in a well-organised mental hospital may be expected to give in due time. What is the quality of the family stock, and what are the natural developments of it, good or bad, under similar and under different conditions of life? It is not sufficient to inquire whether a parent or other near relative was insane, it is necessary to trace out the fortunes of other members of the family who were or were not insane—how they lived and how they died. How is it that, as sometimes happens, one child of the same family becomes insane or commits suicide, another grows to high intellectual eminence, and the third is a hopeless castaway or actual criminal? Certain it is that a congenital moral imbecile, endowed the while perhaps with a singularly acute cunning, yet destitute of the very elements of moral feeling, will be usually found to own an insane inheritance. In what ways, if at all, do the thoughts, feelings and doings of one generation affect the natures of succeeding generations? Is it so certain, as nowadays so confidently assumed, that acquired characters of mind and body are never inherited? What are the periods of physiological development and decline most dangerous to a weak or unstable nature, what the varieties of insanities most likely then to occur, and what the measures—intellectual, moral and physical—best suited to counteract the danger in a particular case? Here, as elsewhere, an *individual psychology* is the special want. What diseases in the parents other than insanities are most liable in breeding to conduce to mental derangement in the offspring? The effects of inter-breeding of different disease-tendencies is a subject which yet calls for and may be expected to repay

systematic study. When the intellectual and moral nature of the individual is viewed as a natural process of organic development, the inevitable product of the nature within and the nature without him, the absolute and artificial division between the physical and moral must needs disappear and the essential unity of mind and body be reflected in one fruitful mental science.

Recognising the unity of body and mind, and viewing mind in its mortal manifestations as the supreme and, so to speak, sublimated expression of vital function, it plainly appears that the study of its unsound manifestations can only become fruitful by means of a thorough and complete observation of all the bodily functions and of all their manifold disorders. Old writers, not without a dim notion of this unity of organic being, set forth the special effects which they supposed the several internal organs to exert upon the moods of mind, enumerating the various so-called morbid humours engendered by them; insomuch that each organ was believed to have its special animal spirit. Which, after all, perhaps, it has in some sort seeing that, besides its specific biochemical function, it may exert its specific organic rhythm. It is certainly not inconceivable that a special organ, thrilling with infinitely subtle motions through every element of it, does radiate fine rhythmical thrills to other special organs in intimate vital sympathy with it. Black bile was the supposed cause of melancholy, as a liver out of order is still the cause of a gloomy depression of spirits. Thus the passions were located in different viscera: courage in the liver, a coward being white-livered, spleen in the spleen, compassion in the bowels, good or bad feeling in the heart. Translate the crude notions into the more positive but still largely conjectural notions of the present day, and they point to the subtle matters of the so-called internal secretions which, directly or indirectly, act upon the brain; not only physiologically in the constitution of the emotions when functions are sound but also pathologically when things go wrong. Courage may not reside in the liver, but when the liver is disordered its representation in the brain where the emotion is kindled and felt answers to the local disturbance; the liver may not have its special animal spirit, but it has its special effect on the animal spirits; may not engender its own "morbid humour," but certainly engenders matters which morbidly affect the mood or humour of mind. These old writers, after all, conceived the general notion of an organism in which all members are members of one body and members one of another; a notion which is apt to be lost sight of nowadays when special physical and chemical researches are pursued with such diligent minuteness and almost expected to explain its mysteries.

Indispensable, however, these minute researches certainly are, and

indispensable the means and appliances of suitable laboratories to carry them out. Into every mental act bodily functions enter, and every bodily function is affected mentally. Exalt the glory and grandeur of mind as we may, the rude fact remains that it is not always either grand or glorious and that its tenure at best is precarious; a defective thyroid notably weakening and almost extinguishing it, and a poison generated by a mishap to one or another of the subtle metabolic processes inflaming it into a delirious mania or precipitating it into a profound melancholia. A complete clinical and pathological study of insanity cannot therefore be made without an adequate knowledge of all the diseases treated in general hospitals and of the morbid effects discovered in their pathological laboratories. That indeed is strong reason why a mental hospital should be near to and in close and constant touch with the medical work and thought of the general hospitals. These on their part might profit by the close intercourse, being incited thereby to study the special mental features of the different bodily diseases, a study hitherto for the most part neglected. Has not every bodily disease perchance its special mental complexion? Unquestionably the distribution of diseases, mental and bodily, into separate tight compartments and the corresponding isolation of minds limited to the study of them contradict the very principle of the unity of body and mind and are fraught with the worst hindrances to the progress of medical science.

Although the clinical study and exposition of mental disorders has always been diligently and profitably pursued, much yet remains to be done. A small hospital filled with a constant succession of patients would evidently afford opportunities of such particular attention to individual cases as cannot well be given in a large asylum crowded with persons in all stages of mental disease for mere detention. Not only because more close and exact observations might be made, but also because the attendance of many persons, physicians and students, stimulating one another by constant intercourse, occupied at the same time with the study of diseases in the general hospitals, would sharpen observation, suggest inquiries, keep fresh the interest, prevent routine of thought, feeling and treatment. The insane patient also could hardly fail to benefit by the surrounding atmosphere of sanity.

Hitherto, perhaps, the tendency has been to make too much of a group of symptoms, putting it into a sort of tight compartment and labelling it with a special name, as though it represented a definite disease; after which it is talked of sometimes as "a clinical entity" or "a pathological entity." As if such metaphysical terms were not pure nonsense or had more than descriptive meaning! Nature, everywhere continuous, nowhere divided into quite separate compartments, has no use

for entities. Such habit tends to hinder a larger and truer view of insanity as a disorganisation of the the mental organisation varying in degree, place and character. Delirium, delirious mania, and acute mania represent different degrees of dissolution of mental forms connected by intermediate states, not really different diseases. In like manner mania and melancholia, although properly divided into classes for descriptive and other purposes, are not separated by distinct lines of division in nature, but merge into one another by gradations; cases frequently occurring which might with equal justice be described as examples of one or the other class. The same person shall pass from one end of the scale of mental disorder to the other. Indeed, the natural course of things is, perhaps, first, melancholic dejection and irritability, then the quasi-convulsive reaction of mania, and finally the devastation of dementia. As the mental organisation, when whole and sound, is a confederation of federal parts, the diversities of its disorganisations naturally present different features according to the place and character of the disorganisation and the consequent symptoms. And as minds, like bodies, differ naturally in structure and development, no two minds nor bodies being exactly alike, it would be strange if they did not differ accordingly when their functions are deranged. Melancholic and pessimistic moods are as natural for the most part in everybody's life as exalted and optimistic moods, and in their extreme degrees mark the opposite moods of different temperaments. No marvel, then, that mania and melancholia sometimes alternate periodically in the unsound mind. Insanity invents no new qualities of mind; it only exaggerates or distorts the natural qualities.

Another want notable in the clinical study of insanity, besides the regular study of the individual character in the particular case and the special causes of its breakdown into the particular mental derangement, is the special conditions under which one form of disorder passes into another form. How is it that one mind falls into a deep melancholia and stays there while another, perhaps without previous apparent depression, flares into mania? What are the exact conditions of things under which melancholia passes into mania in the same person, and conversely of mania into melancholia? How is it that these apparently opposite forms of mental disorder alternate in the same person with the frequency and periodical regularity which they show in so-called *folie circulaire*? And go on alternating then during a long life without so much as any appreciable damage to the mind? What are the varieties of insanity which distinctly denote an insane inheritance? And what the special forms of insanity that are the results of special varieties of unsound ancestry? What, again, the special causes, constitutional and pathological, of the



extraordinary mental elation and grotesquely grand delusions which characterise general paralysis of the insane? These and other easily imaginable questions still await the solutions which they may be expected in due time to receive through patient and systematic study under favourable conditions in a well-staffed and well-equipped hospital.

On the purely practical side it is hardly possible to overrate the good which may be done by individual treatment applied particularly to the susceptibilities of the individual character. To every physician concerned with the insane it must have happened, listening to the sad story of one who had been discharged recovered from a large asylum, to hear a relation of the despairing feelings in the depressing surroundings and under the dreary and monotonous routine of the life there, and the expression, perhaps, of a firm conviction that but for the sympathetic attention and encouragement of a particular nurse or attendant he or she never could have recovered. Again, it notably happens sometimes that a turbulent and aggressive maniac, angrily resenting and violently rebelling against the rude mechanical control of several attendants, yields submission to the quiet tact, patient attention and discreetly sympathetic management of a particular attendant. So much may be done in an asylum, as out of it, by humouring the susceptibilities of the individual. If such tact be necessary in the converse of daily life, as it certainly is—in the family, in the school, with children, with servants, with men and women in all the relations of social life—how much more proper is it in dealing with the exasperated sensibilities of an insane person who has lost his power of self control, is possessed perhaps with suspicions or exalted delusions, and finds himself in a situation of restraint which is utterly unintelligible to him and against which his natural instinct struggles blindly? Or with the despairing melancholic who, believing himself irremediably disgraced in this world or doomed to eternal damnation in a world to come, finds in the cheering tone and apt word of encouragement a gleam of hope partially dispelling the gloom and promising a brighter future. Little confidence would the medical practitioner in attendance on ordinary bodily disease inspire, and small good would he do, who had not the sense and tact to humour the susceptibilities of his anxious and often querulous patient.

A complaint often bitterly made by persons who have been discharged recovered from asylums is of the coarseness, roughness and indifference of attendants, and of the degrading humiliation of being ordered about by them in daily routine like so many sheep, without the least regard to personal feeling. Such system of routine is no doubt more or less unavoidable in a large asylum crowded with patients in all stages of disease, but it is none the less apt to be accompanied by an utter want

of the sympathetic imagination which might realise what the particular patient, not deadened into stolid indifference to his surroundings, may feel. A small hospital might therefore serve also as an excellent training ground for nurses and attendants, who could afterwards go into the service of the large asylums, not only fitted by their training for the bodily care of their patients but imbued with a sense of responsibility to them as mental beings.

Another probable advantage of the close observation day by day of the individual patient would be a perception by physicians and nurses of the favourable psychological moment when at the dawn of convalescence the opportune removal from the asylum to a convalescent institution or to private care might save the tottering reason of the patient who, then awakening to the painful consciousness of his sad surroundings and realising the seeming hopelessness of the situation, might otherwise sink into despair, abandon hope, and gravitate into dementia.

That there are crowds of incurable cases of insanity congregated in large asylums is undoubtedly owing in some measure to the common neglect of early treatment when the malady is most curable. The longer the disease has lasted the smaller are the chances of recovery; and the time soon comes in some cases when, if neglected, there is no remedy. Here, as everywhere, the right treatment is to stop the beginnings of mischief. It may reasonably be expected, therefore, that besides the prevention of incipient insanity by wise counsel and treatment in its out-patients' department, the early treatment of acute insanity in a special hospital will prevent the present necessity and perhaps lasting expense of placing some patients in a lunatic asylum—the very name of which is perhaps a terror, the remembrance a sort of nightmare, and the social consequences a life-long prejudice.

The recent outburst of indignant protest by the neighbours of a large asylum against the permission of an occasional walk outside its grounds to harmless patients was not needed to prove how generally the person afflicted with mental disease is looked on as a sort of social castaway and how prejudicial a stigma rests on one who has been confined in a lunatic asylum. Exaggerated apprehensions of danger and the common notion of insanity as a disgrace to be concealed or put out of sight, rather than a disease to be soon and wisely dealt with, are still responsible for much neglect of early attention and for many impediments in the way of its proper care and treatment. If a mental hospital in close touch with the general hospitals and medical schools helps to instil the notion of disease and to dispel unwarranted prejudices it will not have been built in vain.

## MORISON LECTURES.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.,

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### PATHOLOGY OF SYPHILIS OF THE NERVOUS SYSTEM IN THE LIGHT OF MODERN RESEARCH.

Mr. President and Fellows of the College: Allow me to thank you for the great honour of having been invited to give the Morison Lectures in this ancient College of a city, so long renowned as a great seat of medical science and learning.

In considering the general pathology of syphilis of the nervous system it is not necessary to refer to the different bacterial and other organisms which have been described by various authorities as being the specific agent in the production of the lesions characteristic of this disease before the discovery of the *Spirochaeta Pallida* by Schaudinn. This organism, whether it be, as its discoverer believed, a protozoon or a bacterium or micro-organism between a protozoon and a bacterium, is regarded as the specific organism of syphilis by those best competent to judge, viz., Metchnikoff, Hoffmann, Neisser, Levaditi, Bertarelli, Shennan, and many others. Metchnikoff and Roux were the first to demonstrate experimentally the communicability of syphilis to animals and to show that the nearer the animal approached to man, the more the disease approached in its characters and virulence the human form of the malady. Thus, although other animals, especially apes and anthropoid apes, have been successfully inoculated, the chimpanzee alone reproduces with absolute certainty the human symptomatology. This is as we should expect, for the blood precipitin reaction of this anthropoid approaches most nearly that of man. The experiments of Neisser, Hoffmann, Bertarelli, Levaditi,

and numbers of others have confirmed this important discovery, and many new facts have been added to our knowledge of the general pathology of syphilis by experiments on apes and other animals, and I would mention in particular the important discovery by Bertarelli, who was able to inoculate the spirochaete into the cornea of the rabbit and transmit it through a series of such animals. Levaditi has experimented successfully with the cornea from one of these animals and not only transmitted it through a series of rabbits, but used the cornea infected with spirochaetes to produce an infection of the eyelid of an anthropoid ape. Lastly may be mentioned the important observations upon the biochemical changes in the fluids of the body by the Wassermann, Neisser Brück method of serum diagnosis. Upon this tripod, of the discovery of the specific spirochaete, the communication of the disease to apes and the serum diagnosis, a vast amount of most valuable work rests, the tripod is mutually supporting and every day fresh evidence is forthcoming to strengthen the opinion that the true cause of syphilis has been discovered; that, although as yet no vaccine has been successful, this is no longer a hopeless outlook; and, lastly, a most valuable means of diagnosis of syphilis and parasymphilis has been obtained.

#### THE MICROBIOLOGY OF SYPHILIS.

The *Spirochaeta Pallida* examined in fresh preparations is seen with much greater difficulty than other coarser spirochaetes which may exist in the primary sores on the genitals or secondary papules of mucous surfaces. Hoffmann states in order to find them, it is necessary to seek the edges of red blood corpuscles, to which they often are seen to be attached by one end (a process of chemotropism). It is barely  $\frac{1}{4}\mu$  thick and possesses on an average 8-12 very regular, narrow, and very steep coils, the height of which at the ends diminishes somewhat. (*Vide* Figs. 1, 2, 3, 4, Plate I.) The length of this cork-screw-like organism varies within wide limits, from a few up to 26 coils or even more. Examined with a paraboloidal reflecting substage condenser, by which living organisms appear light on a dark background, the *Spirochaeta Pallida* can be seen to rotate on its long axis and oscillate to and fro with a pendulum-like movement, contrasting thus with the coarser and larger spirochaetes, which have an eel-like movement. An observation of Hoffmann showed that the untreated serum of a syphilitic patient caused a cessation of movement after about a couple of hours.

DIFFERENCE BETWEEN THE SYPHILIS SPIROCHAETE AND OTHER KINDS  
OF SPIROCHAETES.—(Hoffmann).

## SYPHILIS SPIROCHAETE.

## OTHER FORMS.

- |                                                                                                                                                                                                                                                                    |                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>1.—Large size 10–15 <math>\mu</math> on the average, still often more than this. The extreme tenuity of the fibre (<math>\frac{1}{4} \mu</math>). This relation between length of fibre and its thickness is very characteristic.</p>                           | <p>1.—Fibres relative to their length far thicker, therefore they have a plumper appearance; the finer forms are mostly shorter than the sp. pallida.</p>                 |
| <p>2.—Very slightly refractile in fresh preparations, therefore only visible with the best apochromatic lenses.</p>                                                                                                                                                | <p>2.—Strongly refractile, and therefore easily seen in fresh preparations.</p>                                                                                           |
| <p>3.—Ends are pointed, often terminating in long red threads.</p>                                                                                                                                                                                                 | <p>3.—Ends blunt. End threads seldom seen.</p>                                                                                                                            |
| <p>4.—Movements screw-like around this long axis; lateral pendulum movements; movements forwards and backwards still less active, often remains a long time inactive anchored to a blood corpuscle, whilst it exhibits rotatory and slight pendulum movements.</p> | <p>4.—Lateral movement much more active, eel like and sinuous, and more rapid change of position. Anchors to cells much less frequently, and detaches itself quicker.</p> |
| <p>5.—The spiral possesses deep, steep, and very regular coils of cork-screw form. Fibres excessively thin in comparison to the length and depth of the spiral.</p>                                                                                                | <p>5.—Coils flatter, irregular, in many forms (<i>Sp. Dentium</i>) narrower fibres, thick and plump in comparison to the breadth of the coils.</p>                        |
| <p>6.—Relation of the depth to the length of the coils mostly greater than 1, namely, 1.0–1.2; 1.0–1.5.</p>                                                                                                                                                        | <p>6.—The known relation is smaller than 1.</p>                                                                                                                           |
| <p>7.—Great elasticity and retention of the spiral form, therefore with more difficulty deformable.</p>                                                                                                                                                            | <p>7.—Softer and more pliable, therefore the form is more changeable.</p>                                                                                                 |
| <p>8.—Only trifling variations in breadth in respect to the form; only the length therefore, also the number of coils variable.</p>                                                                                                                                | <p>8.—Great variability, all transitions from small to large, from thick to thin examples.</p>                                                                            |
| <p>9.—It is coloured by Giemsa red (general scattered chromidial substance).</p>                                                                                                                                                                                   | <p>9.—Colour more bluish red; nuclear rod or rod nucleolus in plasma often demonstrable.</p>                                                                              |

Schaudinn and Hoffmann were able to prove that the *Spirochaeta Pallida* is found in all cases of syphilis and is never found in any other affections. They also discovered spirochaetes in fresh preparations not only on the surface of the chancres and papules, whether of the skin or mucous membranes, but also in the depths of the tissues and in the juice of enlarged inguinal glands of syphilitic cases. Metchnikoff, Roux, and Levaditi have demonstrated the presence of the spirochaetes in chancres on the face and penis of monkeys in association with other organisms; they also found the spirochaete in papules. Buschke and Fischer discovered spirochaetes in abundance in the liver and spleen of an infant affected with congenital syphilis, and Levaditi demonstrated numbers of

spirochaetes in the fluid contained in the bullæ of pemphigus occurring in a congenital syphilitic infant. Since then an ever increasing army of workers have, with a few notable exceptions (Saling Schulze), supported the discovery of Schaudinn. In fact, this organism has been shown in every possible lesion which is definitely syphilitic. In some cases they cannot be found in the primary sore unless a very careful search is made, and even then the search may not be successful. The same applies, with even more force, to the secondary eruptions.

The spirochaetes have been discovered in the capillaries of the skin and in the perivascular tissue. Although only occasionally found in the blood, the spirochaetes are more numerous in the lymph and lymphatic organs in general, and, according to Metchnikoff, their presence in lymphatic vessels may be said to be constant in syphilis, and it is at times possible to see a very large number in the perivascular spaces, although their number in the corresponding blood vessels may be exceedingly limited. I have examined a number of primary sores, mucous tubercles, and cutaneous papules sent to me from the Lock Hospital and in all cases smears have shown spirochaetes by the Giemsa method,\* sometimes, however, only after long and diligent research. In one case of secondary papules I found the spirochaetes by Levaditi method,† although I was unable to find them in the blood (*vide* Fig 7, Plate I.). When the disease becomes generalised and there is a polyadenitis, the organism can be found in glands far removed from the primary lesions; thus Lewandowsky found spirochaetes in the juice of the epitrochlear gland. It is presumed that for a short time, perhaps some hours, the organisms remain in the lymph clefts and spaces of the tissues at the point of inoculation; there it multiplies, and in a short time extends into the lymphatics and produces microscopic changes, although microscopic changes are not visible. In confirmation of this it may be mentioned that Levaditi and Yamanouchi have inoculated the chimpanzee with syphilis, and at a time when the point inoculated did not show the slightest microscopic indication of primary syphiloma they were able to

\* *Giemsa Method.*—Make a film by expression and expose immediately to osmic acid vapour for two minutes. Dry in the air; then place in solution containing one drop Giemsa stain to 1 cc. distilled water for several hours. Wash in water and decolourize in solution of 5 per cent. tannin for some minutes. Wash again in water, and finally in absolute alcohol.

† *Levaditi Method.*—The tissues are fixed in 10 per cent. Formol for 24 hours or longer, and then left overnight in 95 per cent. alcohol, after which they are placed in distilled water until the pieces sink. They are then placed in 1.5 per cent. solution  $\text{AgNO}_3$  90 cc., Pyridin 10 cc., for 2 to 3 hours at room temperature, and 3 to 5 hours in a dark oven at  $45^\circ$  to  $50^\circ$  C. The tissues are then directly transferred to a solution containing 85 cc. (4 per cent. Pyrogallie acid solution, 90 cc., acetone 10 cc.) and 15 cc. pyridin, in which they remain overnight. They are then washed in distilled water, hardened in increasing strengths of alcohol, embedded in paraffin and sections  $5\ \mu$  to  $10\ \mu$  in thickness cut. These are stained by Polychrome methylene blue and differentiated with dilute glycerine, ether mixture, or tannic acid solution. Other authors use 1 per cent. Toluidin blue or Iodine green.

detect an active pullulation of spirochaetes and specific histological changes. The same investigators have recently published some very interesting researches upon incubation in syphilis. These observers have conducted a series of observations on keratitis in the rabbit induced by introducing a small portion of an infected cornea into the anterior chamber of the eye and by killing the animals at varying periods of time afterwards. They have also introduced the infected cornea of the rabbit beneath the skin of the eyelid in apes and a chimpanzee, and examined the tissues of spirochaetes by the Levaditi method. They have formulated the following conclusions. The period of inoculation which precedes the manifestation of the primary syphiloma of the monkey and the specific keratitis of the rabbit is not due to the existence of an evolutionary cycle of the *\*Treponema pallidum*. It corresponds to the slow but progressive histological lesions provoked by the pullulation of the microbe of syphilis. This pullulation is not marked at first, in consequence of a defective assimilation caused, on the one hand, by a change of medium, and, on the other, by the conditions which preside over the supply of nutritive materials. But, as soon as the vessels and new-formed cellular elements assure to the treponemes the nutritive principles of which it has need, the multiplication by the parasite becomes active, and puts an end to the period of incubation.

The organisms after local development at the point of inoculation in man and in the anthropoid ape soon reach the nearest lymphatic glands, where probably they again multiply in the lymph sinuses and spaces, setting up an adenitis; these changes may be biological, provoked by the organism for its perpetuation, and not, as taught, in the nature of a defence on the part of the tissues against the invasion by the organism. The living organism usually prevails and passes into the general lymph stream, causing polyadenitis and an infection of glands remote from the seat of inoculation. The organisms may thus find their way into the thoracic duct, and a general infection of the blood stream takes place, with the development of the secondary eruption (roseola). Moreover, a profound biochemical change occurs in the blood and fluids of the body (*vide* p. 30). Occasionally, as first pointed out by Lang, and as I myself have observed in several cases quite early in the disease, even before the primary sore is healed, symptoms pointing to meningitis may occur; also, as will be pointed out later, and which I have seen illustrated by many examples, the most severe and the most intractable cases of brain and spinal syphilis occur within the first twelve months after infection; it is quite probable that

\* Some authors prefer this name to *Spirochaeta Pallida*.

the meninges were infected at the time of the roseolar rash in some of these cases, but the symptoms occurring then were slight and overlooked. Not infrequently severe symptoms of meningitis have occurred within a few months of the primary sore. It is reasonable to suppose that if the spirochaete is the cause of the secondary cutaneous eruption by a sort of metastatic process in the skin capillaries, that the same may occur in the meninges. The following case reported by Gautier and Maloizel is interesting in this respect, and tends to support that conclusion. A young woman affected with secondary syphilis had seven successive attacks of cutaneous eruption, simultaneously with sudden fever, headache, stiffness of the neck, and vomiting, accompanied by lymphocytosis of the cerebrospinal fluid; a complex of symptoms of syphilitic meningitis. Again, Boidin and Weil have reported a most interesting case of a young man, aged 18, who had (1) a hard chancre in the middle of June; (2) headache the middle of July; symptoms of meningitis and lymphocytosis of cerebrospinal fluid August 5th; roseolar rash August 12th. Cure of the meningitis by inunction August 17th. (See also a case of mine, page 37.) It is a pity that some of the fluid of such cases was not used for experimental inoculation of an ape. So far only Hoffmann has succeeded in showing that the cerebrospinal fluid may be infective, for he has successfully inoculated a monkey with the cerebrospinal fluid obtained blood free and taken with all precautions from a man suffering with a papular syphilide. Neisser states that Dohio and Tanaka have found spirochaetes in the cerebrospinal fluid in the case of a patient with a papular eruption; a second examination, as well as one by Neisser himself, was unsuccessful. It may be that centrifuging a fluid of such low density would disintegrate such delicate organisms. Again, we know that it is not infrequently impossible, except by culture or inoculation, to find tubercle bacilli in the cerebrospinal fluid of tubercular meningitis. Until experimental investigations have been made with fluid obtained from early acute cases of syphilitic meningitis, the absence of the organisms upon microscopic examination and failure of experimental inoculation is no valid argument against their being the cause of the meningitis. It may be said that if the spirochaetes are the cause of the meningitis, they could be shown in sections or in films of the exudation. It is seldom that syphilitic meningitis is rapidly fatal, and cases would rarely come under early enough observation; moreover, not more than 1 or 2 per cent. of syphilised persons suffer with *obtrusive* symptoms of meningitis, and they seldom die in consequence thereof, and still more rarely do they die for at least some months after the onset of symptoms. I have been unable by the silver or Giemsa method to find spirochaetes in the exudation of typical cases of syphilitic mening-



itis. But I was unable to find trypanosomes in the similar cell infiltrations of the meninges and perivascular spaces of sleeping sickness although I have examined quite a thousand sections obtained from thirty cases. Yet, it cannot be doubted that the *Trypanosoma Gambiense* is the exciting cause of the meningo-encephalitis.

Syphilis is characterised by being an eruptive malady following the inoculation of the virus, presumably the spirochaete of Schaudinn, and by the possibility during the remainder of the life of the individual of fresh eruptions occurring in connection with the existence of the virus in the body. A blow may be followed by a gumma, or a syphiloma may occur spontaneously in any part of the body at any period of time after infection. Microscopic examination shows that essentially the same tissue reactions occur in these late manifestations of syphilis as in the primary or secondary stages. It is well known that tertiary lesions are, as a rule, non-infective; consequently, we should not expect to find the active agent, or what we believe to be the active agent—*Spirochaeta Pallida*—except in a few instances, and then only in small numbers. This is actually what has occurred. For a long time attempts to prove the existence of the spirochaetes in tertiary lesions failed, and this led to the not unwarrantable view (which may be true) that the organism may exist in a latent and attenuated, possibly intracellular form, and it is possible that late manifestations may be the result in some cases of secondary lesions which have remained latent until raised into activity by some exciting factor, such as exposure to cold, trauma, and toxæmia—microbial or otherwise; for, at no period after infection may such syphilitic meningitis occur. On p. 58 I have described a case of congenital syphilis in which cerebrospinal meningitis occurred in a girl of 16. I was unable, however, to find spirochaetes, although the meningitis was very active and typically syphilitic in its histological character. It must be admitted that this is a part of the microbiology which is unsatisfactory. The spirochaete, however, has, in a few instances, been found in a gummatous tumour. Schaudinn found it in a gumma of the liver. Blaschko recently claims to have discovered spirochaetes in serotal papules which occurred sixteen years after infection. Reuter and Schmorl claim to have found spirochaetes in syphilitic aortitis embedded in the proliferated intima between the fibrils, sometimes in places in which regressive changes are absent. Moreover, Benda claims to have demonstrated typical spiral, straight and granular forms of the spirochaetes in the external layer of the media, and still more in the connective tissue adjacent to a patch of syphilitic endarteritis. Just as there are, relatively, but few successful observations proving the existence of spirochaetes in tertiary lesions, so there are, relatively, few

successful experiments of inoculation of animals from tertiary lesions. Hoffmann has, however, succeeded in inoculating an ape from a gumma occurring in a man three and a half years after primary infection. It has already been stated that the *Spirochæta Pallida* is an organism between a bacterium and a protozoon, and in spite of the divergent views respecting the classification of spirochaetes, there are, in my judgment, more characters linking them to the protozoon than to the bacterium. The *Spirochæta Pallida* contracts, moves, and modifies its structure in a manner different to a bacterium. The appearance of resting forms is totally different, and they arise in a different manner to the spores of bacteria (Prowazek). Again, the clinical aspect of affection from spirochaete invasion differs from that of bacterial diseases, and conforms especially to certain trypanosome infections. There is a periodicity of the symptoms altogether unknown in bacterial diseases. But, what has struck me from my own personal experience and knowledge, is the great similarity of the histological lesions of the nervous tissues of chronic trypanosome infections, *e.g.*, sleeping sickness and dourine, to syphilitic and parasymphilitic lesions. (*Vide* Figs. Plates II. and III.). The universal perivascular infiltration of lymphocytes and plasma cells in the central nervous system was thought by Nissl and Alzheimer to be pathognomonic of general paralysis and syphilis, but I have shown that exactly the same occurs in sleeping sickness. In the *mal de coit* of horses an ataxic paraplegia occurs, and I have found posterior root degeneration and sclerosis of the posterior columns in five cases of dourine sent to me from the Imperial Bacteriological Institute of India by Dr. Lingard. In all chronic trypanosome infections, *e.g.*, sleeping sickness and dourine, I have found a marked hyperplasia of neuroglia, and in experimental sleeping sickness of apes, as I shall show you, this connective tissue hyperplasia preceded the perivascular infiltration. Thus we see that in both syphilis and trypanosome infections we have a hyperplasia of the fixed tissue cell elements, endothelial and conjunctival, with little or no polymorphonuclear reaction. Moreover, Spielmeyer has obtained by experimental trypanosome infection of dogs, a lesion of the posterior columns of the spinal cord simulating the ataxic lesion; he has also produced optic atrophy. Again, there is a similarity in the fact that lymphocytes and plasma cells are found in the cerebrospinal fluid of trypanosome diseases of animals and man, *e.g.*, sleeping sickness. Moreover, Levaditi has shown that, in point of view of sensibility in respect to hæmolysing poisons, blood corpuscles, spirochaetes and protozoa constitute a homogeneous group, and the spirochaetes correspond in this respect more to the protozoon than the bacteria.

The study of all these diseases is primarily biological. The conta-

gium vivum is a living organism whose activities, like that of all living organisms, are for self-preservation and the preservation of the species. The chemical toxin which the organism produces is to enable it to live and multiply. The spirochaetes consist of a viscid plasm covered with a membrane which serves as a means of osmosis. This osmotic membrane is a lipoid substance, like that which forms the membrane of the red corpuscles, and is sensitive to hæmolysing substances.

The fact that Castellani has discovered a spirochaete which he terms *Sp. Pallidula* in yaws is of importance in showing that a spirillary organism not quite morphologically identical with that of syphilis is probably capable of producing a chronic disease in many of its features not unlike syphilis. It might be argued that all the postulates laid down by Koch have not been fulfilled, and, therefore, that we have no right to claim that the *Spirochaeta Pallida* is the specific organism of syphilis. Thus the organism, although it has been grown in celloidin capsules, has not been cultivated on an artificial medium outside the body, and the disease reproduced by injection of such a culture. But the same argument might be applied to certain established protozoal diseases, *e.g.*, malaria and sleeping sickness. Dourine may almost be regarded as the syphilis of equines, for it is characterised by an infective sore on the genital organs, affection of the nearest lymphatic glands, then infection of the blood stream followed by successive eruption of plaques; and, as in syphilis so in dourine and sleeping sickness, the juice of the lymphatic glands, in a condition of acute swelling, shows the specific organisms more readily than the blood films. The trypanosomes may disappear from the blood entirely, even without the administration of drugs, and reappear, giving rise to an irritating eruption of papules and fever, and the trypanosomes can be found in smears obtained by scarifying the papules more readily than from smears of the blood. This was demonstrated by Lingard in the case of *mal de coit* of horses, and by the French observers in a case of sleeping sickness. So, also, in syphilis I have been able to find an abundance of spirochaetes in the secondary papules of the skin, although I was unable to find them in the same cases in the blood films (*vide* Fig. 7, Plate I.). It is a remarkable fact that Neisser was unable to inoculate animals by injecting the virus into the blood or into the organs; success was only obtained by scarifying an epiblastic skin surface and rubbing in the virus. This is precisely the seat of eruptions and pullulation. It looks as if the organism, to perpetuate the species, must find its way out of the body in the way it came in. Sir Patrick Manson (Huxley Lecture) expressed the opinion that, by analogy, we must presume that all trypanosome diseases are carried by some biting insect which acts as alternate host. But dourine spreads in the same way as syphilis. It is quite

possible that the *Trypanosoma Equiperdum*, which differs very little from the *Trypanosoma Evansii*, may be this trypanosome which has acquired the habit of pullulation in the mucous cutaneous orifices, and when infection occurs, always tends to get back there. In syphilis the same habit may have been acquired. It is known that mucous tubercles and condylomata (secondary eruptions) are more infective than the primary sore, and contain immense numbers of spirochaetes. Similarly, upon reading Lingard's experiments, I find he mentions that the *Trypanosoma Equiperdum* was found in great abundance sometimes in the vaginal mucus when it could not be found in the blood. Again, he was more successful when he inoculated animals by scarifying the genitals and inoculating with blood from a papule or with vaginal mucus than when he injected the blood into animals. Those facts accord very much with Neisser's experiments, and would seem to indicate that a habit had been acquired by the *Trypanosoma Equiperdum* of developing in the mucous membrane of the genital organs and of using this acquired habit as the means of preserving the species.

Finally, the therapeutic agents, mercury and arsenic in the many forms employed, are specific for both trypanosome and spirochaete affections. They are not of much use for bacterial infections. Mercury, particularly in the form of inunction, is especially valuable, and this may be owing to the fact that it prevents the pullulation of the spirochaetes on the surface of the body, including the mucous orifices, a habitat which these organisms have found particularly favourable for perpetuation of the species by transmission to another individual. Mercury, moreover, administered in any way, tends to come out by the skin, as can be readily demonstrated.

I have pointed out that, practically, the morbid tissue changes in syphilis are similar, whether the lesion be the primary sore or a gumma twenty years later; moreover, it is difficult to understand how the spirochaete, seeing that it has hardly ever been found in tertiary lesions, can produce the same specific cell hyperplasia so long after the primary infection. The following hypotheses may be put forward to explain the phenomenon of a gumma appearing spontaneously in the central nervous system long after the primary sore and apparent cure of the disease:—

1. The spirochaete, or some modified form of it, has remained latent in the tissues at the seat of the lesion, and, for some reason, inherent or otherwise, the resistance of the tissues at that particular spot has become lowered, and the organism has exerted again its specific activity - possibly in some not yet discovered intracellular form.
2. The specific organism has remained latent in some other tissue, *e.g.*, the marrow of bone, the spleen or glands, and, escaping into the

blood or lymph circulation, has, like a new growth, engendered a metatasis, which has developed and increased, producing a hyperplasia of the fixed tissue cell elements conjunctival and endothelial.

3. There may be varieties of specific spirochaetes, one of which may have an elective affinity for the central nervous system, as we know the *Trypanosoma Gambiense* has. It is difficult to differentiate this trypanosome from other forms by morphological appearances (*vide* Figs. 4 and 5, Plate I.) ; how much more difficult would it be to differentiate varieties of *Spirocheta Pallida*.

4. The invasion of the body by the spirochaetes has altered the blood and lymph biochemically, so that the tissue reactions to all causes which would lead to injury may take on the specific character.

Thus a blow on the head, vascular-stasis, or some inherent weak spot may become the seat of a gummatous process. Although we are only beginning to unravel these biological problems, the evidence so far appears to be in favour of the fixed tissue cell hyperplasia with subsequent necrobiosis and fibrosis being a reaction to the influence of the specific organism. The fibrosis may be regarded as the attempt on the part of the tissues to repair the damage done in the struggle between the specific virus and the tissues; it is accomplished by the young connective tissue cells which have survived the fray; these are converted into fibroblasts and eventually into sclerous fibrous tissue. The amorphous caseous material is the residuum of the dead cells and organisms, especially the former, which, owing to the toxic influence of the virus and the cutting off of the vascular supply, have undergone nucleolysis and plasmolysis. The organisms, when found, are not discovered here when the struggle is past, but at the growing edge, where the new blood vessels and embryonic cell hyperplasia is most active; for it is here that the organism finds pabulum for its multiplication.

## PLATE I.

FIG. 1.—*Spirochaeta Pallida* in smear preparation of condyloma, stained by Giemsa solution. Magnification 3,100.

FIG. 2.—Another portion of the smear showing appearances of two spirochaetes twisted around one another; possibly this is the result of longitudinal fission. Magnification 3,400.

FIG. 3.—*Spirochaeta Pallida* from smear preparation of mucous tubercle. Magnification 1,800.

FIG. 4.—Section of spleen from a case of congenital syphilis, stained by Levaditi method. Magnification 1,400.

FIG. 5.—Blood smear from a case of sleeping sickness, showing *Tryp. Gambiense*. Magnification 2,000.

FIG. 6.—Blood film showing *Tryp. Brucei*. Magnification 1,700.

FIG. 7.—Section, showing spirochaetes, of a papule of skin from a case of secondary syphilis, before mercury was administered. Stained by Levaditi method. Magnification 1,000.

It will be observed that it would be difficult to decide the nature of the two trypanosomes by morphological characters alone.

PLATE I.

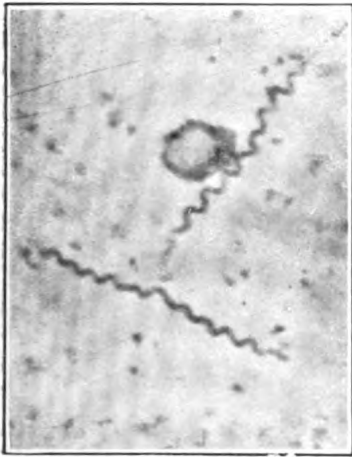


FIG. 1.

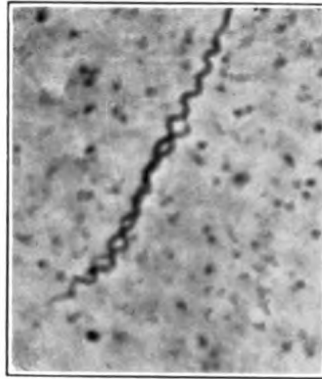


FIG. 2.



FIG. 3.

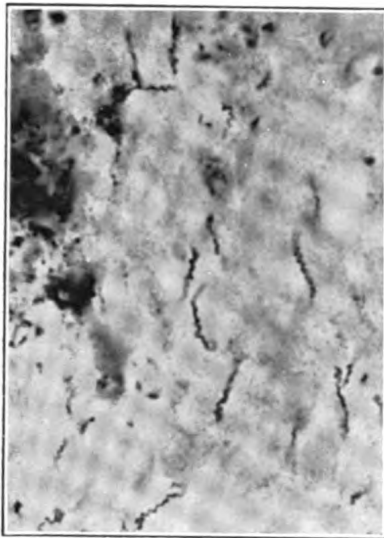


FIG. 4.

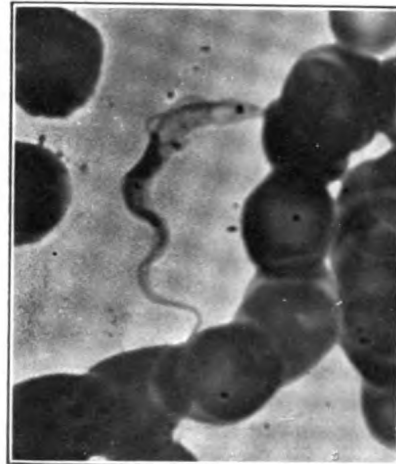


FIG. 5.

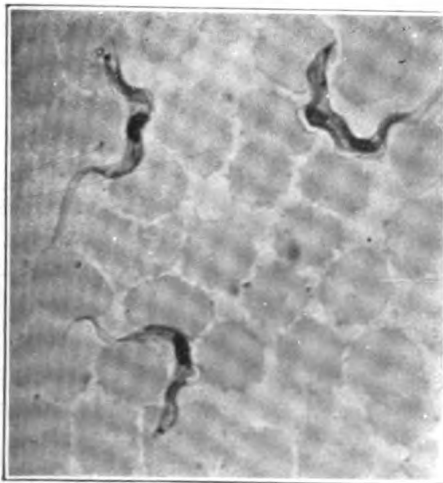


FIG. 6.

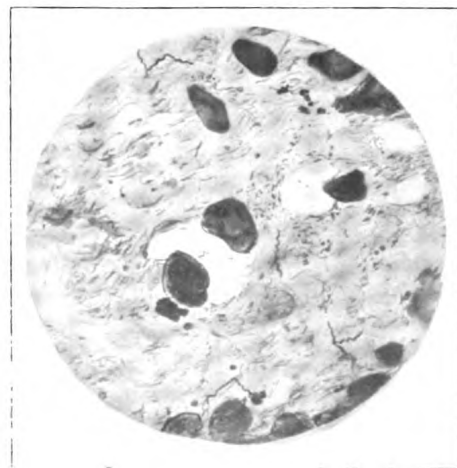


FIG. 7.







PLATE II.

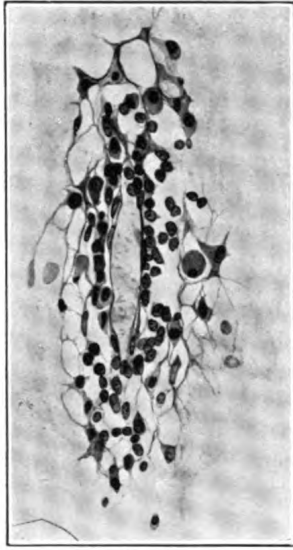


FIG. 1.

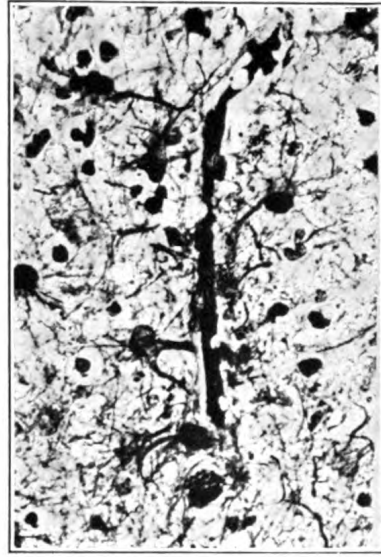


FIG. 2.



FIG. 3.

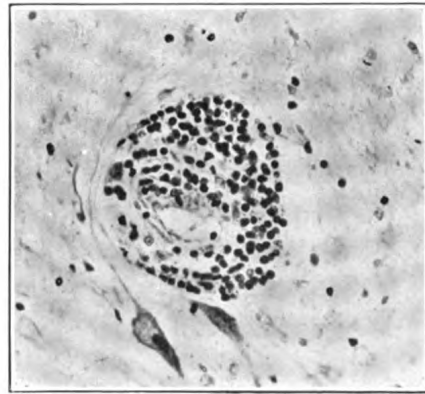


FIG. 4.

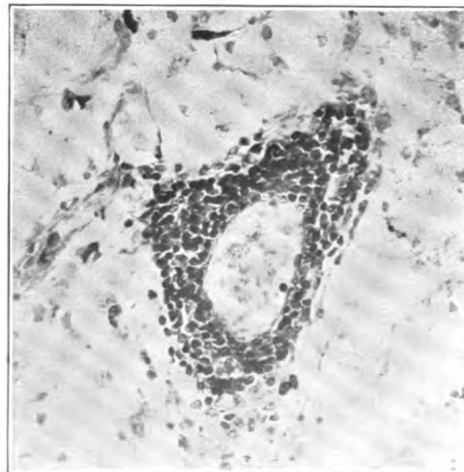


FIG. 5.

## PLATE II.

- FIG. 1.—Section of a small vessel showing the sheath infiltrated with lymphocytes and plasma cells, and with proliferated glia cells. Experimental sleeping sickness in an ape. Magnification 320. (Cf. Fig. 3, Plate III.)
- FIG. 2.—Section of cortex cerebri from a case of sleeping sickness in a European. Stained to show the neuroglia. Magnification 450.
- FIG. 3.—Section of brain of ape infected with *Tryp. Gambiense*, showing perivascular neuroglia cell hyperplasia. Below are seen a series of neuroglia cells in various stages of development. Magnification 320. (Cf. Fig. 4, Plate III.)
- FIG. 4.—Perivascular infiltration with lymphocytes and plasma cells from a case of gummatous cerebrospinal meningitis. Stained by polychrome blue. Magnification 250.
- FIG. 5.—Section of central nervous system from a case of sleeping sickness in a European, showing perivascular infiltration with lymphocytes and plasma cells. Magnification 250.

## PLATE III.

- FIG. 1.—Photomicrograph of a section of the ascending parietal convolution in a case of tabo-paralysis of four years' duration, showing a small vein surrounded by plasma cells, which are lying in a dilated lymphatic. The vessel at another part had ruptured and filled the lymphatic sheath with blood corpuscles. Some of the large swollen cells showed in their interior the blood pigment in various stages of destructive disintegration: they appear to have, therefore, a phagocytic function. Nissl stain. Magnification 500.
- FIG. 2.—Section of syphiloma of the brain showing vessel with (*e*) thickened endarterium. (*l*) lymphocytes, (*p*) plasma cells. Magnification 300.
- FIG. 3.—Section of small subcortical vessel, acute general paresis. (*l*) lymphocytes, (*p*) plasma cells. Magnification 300.
- FIG. 4.—Small vessel, acute general paresis, showing neuroglia cells with proliferating nuclei and processes extending on to the small vessel. As in sleeping sickness there is little or no infiltration around because there is no pial or lymphatic sheath. Magnification 400.

PLATE III.

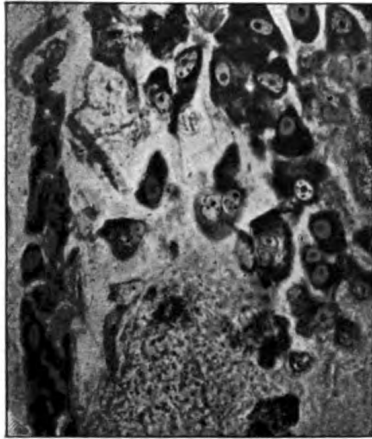


FIG. 1.

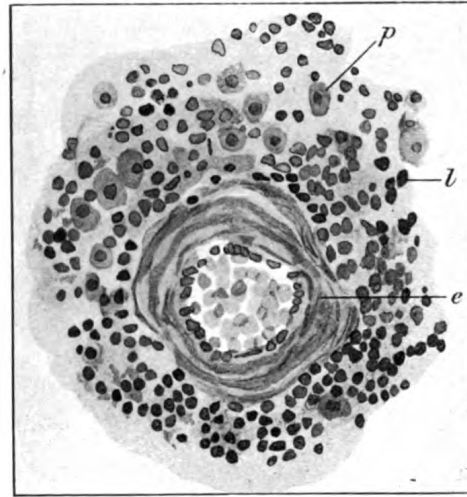


FIG. 2.

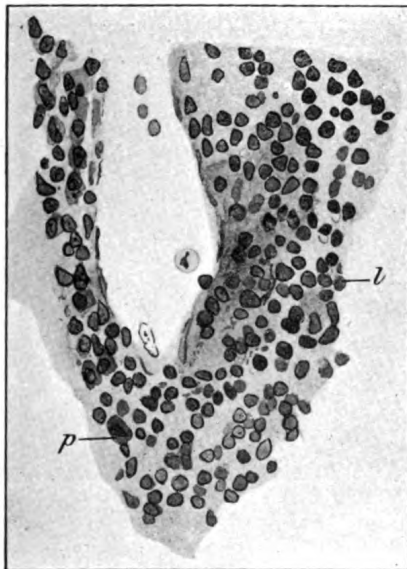


FIG. 3.

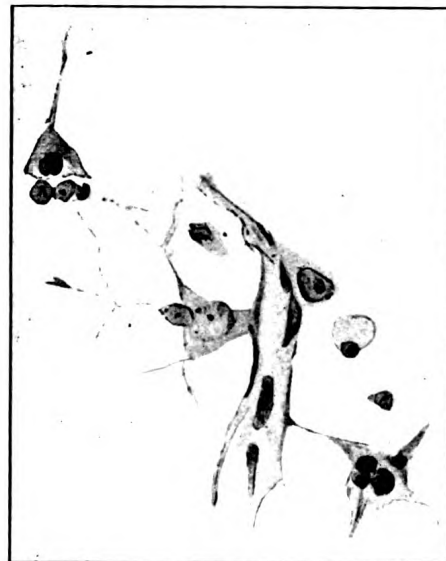


FIG. 4.



## LECTURE II.

In my last lecture I endeavoured to point out some facts and hypotheses of the biological problems of syphilis, especially in relation to disease of the nervous system. To-day I wish to draw your attention to modern researches bearing upon the bio-chemical changes which occur in the tissues and fluids of the body as a result of the entry and persistence of the syphilitic virus in the body.

I must, however, first make a slight digression, in order that you may obtain a better understanding of the altered bio-chemical conditions; this digression refers to the nature of lipoids, substances which have recently, in connection with hæmolysis, attracted a great deal of attention (and I wish here to acknowledge my indebtedness to Dr. Rosenheim for valuable information). "There seems to be a good deal of truth in the opinion of Bang that the importance of protein as carriers of life ("Träger des Lebens") has been over-estimated, while that of the lipoids has been neglected." Pflüger, and most physiologists, have taught that the vital activities depended essentially upon proteins. Bang contested this exclusive view. The name lipoid was given by Overton to *fat-like* substances which are contained in the cells of all living things, animal and vegetable. They were named by Waldemar Koch, lecithans, but this name has not been adopted. These lipoids may be divided into three groups (1) N. and P. free Cholesterin, fatty acids, and lipochromes; (2) Nitrogenous but P. free Cerebrosides; (3) Phosphatides containing both N. and P.; of these, the most important are the mono-amino phosphatide *lecithin* and the di-amino-phosphatide *sphingomyelin*.

These lipoids were, until recently, considered of little importance; in fact, cholesterin was looked upon as a physiological curiosity by virtue of the fact that its crystals had a chip out of one corner, and little else was said about it except that it was contained in the red blood corpuscles and formed the principal constituent of gall-stones. Lecithin was known to be a constituent of the red corpuscles, but it was not until Flexner and Noguchi's experiments on cobra venom had been published that the importance of these bodies in the action of toxins aroused attention. They found that cobra venom contains two poisons, a neuro-toxin and a globulin which has the property of dissolving red corpuscles. If, however, they washed the red corpuscles free of serum, the cobra venom no longer had a hæmolysing action; but, on adding serum to the washed corpuscles, an addition of the cobra venom produced hæmolysis. Clearly something was contained in the serum which interacted with the venom to produce the result. Kyes showed that the activator is soluble in alcohol and in ether, and he finally identified the substance as lecithin. But cholesterin, another

lipoid, has the property of counteracting the activating effect of lecithin on cobra venom. This antagonism of cholesterol and lecithin points to some bio-chemical or bio-physical relationship between the two bodies. Moreover, this relationship as regards osmotic membranes and hæmolysis has been experimentally put to the test by Panucci. This observer constructed glass cells covered with a membrane impregnated with lecithin and cholesterol; in these he placed hæmoglobin solution and then suspended them in the toxin solution; the hæmoglobin behaved differently

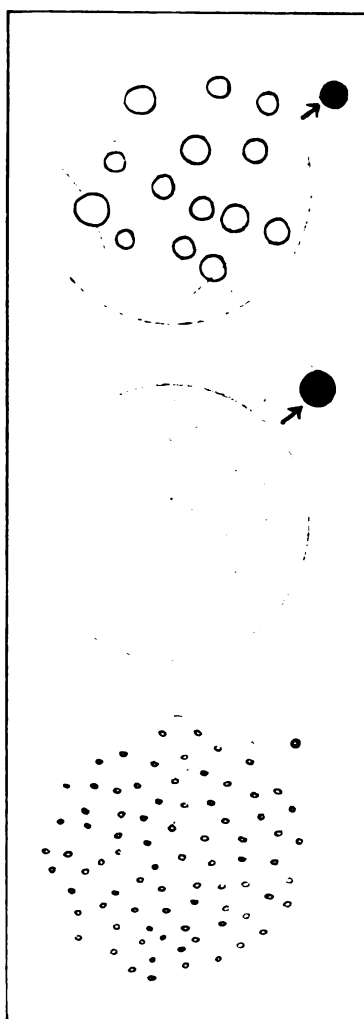


FIG. 1.

- (a) Normal blood corpuscle with osmotic membrane permeable to ions of Na, K, Ca.
- (b) Chemical explanation of hæmolysis by dissolution of osmotic membrane and escape of hæmoglobin.
- (c) Physical explanation of hæmolysis by a bio-physical alteration of the osmotic membrane, by which it becomes permeable to the large hæmoglobin molecules.



(as regards diffusion) according to the proportions of these substances in the membrane. If we regard the red blood corpuscles as consisting of a sponge-like protein stroma holding the hæmoglobin in solution, the whole being covered with a membrane consisting of a properly adjusted complex of the lipid substances, cholesterin and lecithin, then we may suppose that hæmolysis occurs as a result of a chemical or physical disturbance of the balance between the cholesterin and lecithin. In hæmolysis the membrane is either dissolved by the action of a ferment or a physical change occurs in the membrane, by which it becomes permeable to the large hæmoglobin molecules, whereas in its natural perfect state it will only allow the smaller ions, Ca, Na, and K, to pass through. (Fig. 1.) It is probable that all cells and unicellular organisms possess similar osmotic membranes, and that the lysis of these organisms depends upon physical or chemical changes, in the osmotic membrane which is termed a periplasium. The importance of this question is obvious in regard to cytolysis, bacteriolysis, and protozoolysis, and it will become especially apparent when we come to the study of the Wassermann reaction of the deviation of the complement in the sero-diagnosis of syphilis.

In regard to the origin of lipoids, especially in pathological conditions, it is necessary first to refer to an important paper by Munk just published. This observer has used the polarising microscope to distinguish between fat and lipoids in cells; the latter are doubly refractile when the Nicol's prism is rotated. Ambrose and Held made use of this method for determining the existence of the myelin sheath in the anterior and posterior roots of the embryo. Munk finds that the existence of lipoid droplets in the cell is associated with dissolution of the nucleus and destruction of the cell. Rosenheim remarks that the phosphatides may form a link with the cell nuclein which possibly obtain their necessary supply of phosphorus from this source. A lipoid substance in great abundance, then, means cell dissolution; the nucleus highly charged with phosphorus and the cell protoplasm break up into a lipoid complex as a result of the nucleolysis and plasmolysis. It may be suggested Levaditi's experiments show that the spirochaetes stimulate the fixed tissue cells to proliferate, and then, invading this bed of young cells rich in nuclein, they, by the action of some secretion or otherwise, cause these same embryonic cells to undergo lysis, thus providing the necessary pabulum for their own growth and proliferation. It is probable these young cells are more easily attacked than the older cells, and this may be the reason that the spirochaetes are found in such great abundance in foetal tissues, and why the foetal tissues, especially the liver, contains such an abundance of lipoid substance serving for the Wassermann reaction, although chemi-

cally it does not differ from lipoid substance which can be obtained from normal tissues.

We are now in a better position to consider the serum diagnosis by the Wassermann and other methods dependent upon bio-chemical changes induced in the body by the introduction of the syphilitic virus whereby immunity to future inoculation is effected; and which, in my opinion, lies at the root of the late degenerative processes occurring in the central nervous system, and which are collectively termed parasyphilitic.

Although it has now been ascertained that the syphilitic virus induces in the body metabolic changes whereby larger amounts of lipoids occur in the serum, and also in the cerebrospinal fluid in general paralysis and tabes, yet these same lipoids are found in the normal tissues and fluids, the specific character is manifested by quantity rather than quality. The substances which in hæmolysis play the part of *antigens* are lecithins, combined with other substances, especially soaps (Rondoni and Sachs), and those which play the part of *antibodies* are possibly complexes of lipoids and globulins. Yet, although in describing the Wassermann and other methods and the evolution of the knowledge concerning the same the terms antigen and antibody will be used, it is better to state at once that they do not conform to the antigen and antibody of bacteriolysins, and that the deviation of the complement (or fixation of the complement) may possibly depend upon the presence of those two kinds of lipoids, which we have previously seen play such an important part in the action of cobra venom.

#### THE SERUM DIAGNOSIS OF SYPHILIS BY THE WASSERMANN METHOD.

To explain the principles of this method it is necessary to make a few introductory remarks regarding its origin. Bordet, in 1901, discovered the phenomenon known as the absorption or deviation of the complement. At about the same time Gengou discovered a similar phenomenon when working with precipitins. Wassermann, Neisser and Brück, Levaditi, Citron, Plaut, Stertz and others have applied this method of the absorption of the complement of Bordet and Gengou to the diagnosis of syphilis by the existence of syphilitic antibodies and antigens in the blood serum and cerebrospinal fluid of persons suffering with primary, secondary and tertiary syphilis, as well as in the post-syphilitic, parasyphilitic (or late syphilitic) affections, viz., tabes and general paralysis. The epoch-making experiment of Pfeiffer on bacteriolysins may be said to have afforded the foundation of our knowledge of the principles governing immunity. Bordet, by his observations, came to the conclusion that bacteriolysis by the serum of an immunised animal was due to the presence of two substances, the one destroyed by heat (thermolabile)

present in normal serum, the other (thermostabile) a substance which resisted heat ( $56^{\circ}$  C.) and was only present in the body fluids and blood of an immunised animal. The former is called the cytase or complement, the latter the immune body or antibody (amboceptor, Ehrlich).

Bordet and others, by experiment, found that if the corpuscles of one animal were injected into another of a different species, these corpuscles disappeared with the production in the serum of a specific hæmolysin analogous to the bacteriolysin; the hæmolytic properties of the serum being due to a specific antibody (immune body) linking up the cytase or complement to the corpuscles. This important discovery led to the possibility of the study of the theory *in vitro* and its practical application to the diagnosis of disease. The same principles determine the production of hæmolysins as bacteriolysins, and the solution of experimentally sensitised corpuscles can be used as a precise index of the presence or absence of one of the two unknowns, viz.: (1) the antigen; (2) the antibody or immune body. The thermo-labile substance cytase (Bordet) complement (Ehrlich) is contained in normal serum. Bordet holds that there is only one complement in normal serum, and, contrary to Ehrlich, that it is not a specific substance for each antigen, but specific for each animal. Bordet has introduced the terms antigen and antibody, the former to signify any substance which, when injected into an animal, will cause the production of an immune serum; the latter to denote the antagonising substance produced and which is the essential for the immunising action of the serum. Now, if either the antibody or the complement be not present, or be removed, the specific bacteriolytic or hæmolytic action of the serum or fluid is lost. Again, if the antibody in the presence of the complement is linked up to the antigen, both the antibody and the complement will be inactivated. To find out if a given serum or fluid, *e.g.*, cerebrospinal fluid, contains either the antigen or the antibody is by the experimental inductive method known as the *deviation of the complement*. How is this effected?

We require first to immunise an animal against the blood of some other animal; for this purpose the blood corpuscles of a sheep are injected into the circulation of a rabbit. The blood serum of the rabbit is thus made hæmolytic to the corpuscles of the sheep by virtue of an immune body *plus* the normal complement or cytase. The latter can be removed by heating to  $56^{\circ}$  C. for 30 minutes without destroying the former. We have thus the immune body, which by itself will not dissolve the washed corpuscles of the sheep. If, however, we add the normal serum of a guinea pig, the amboceptor or immune body links up the complement or cytase and the corpuscles are dissolved.

The second part of the experiment is the deviation of the complement or its neutralisation, so that hæmolysis no longer takes place when the serum of the guinea pig is added to the immune body and the washed sheep's corpuscles. This is effected by the presence of both antigen and antibody in the fluid to be examined. The serum, or cerebrospinal fluid, to be examined is mixed in varying dilutions with a watery (or alcoholic) solution of the liver of a syphilitic fœtus, which will contain the antigen (lipoid). A small amount of the serum of a guinea-pig is then

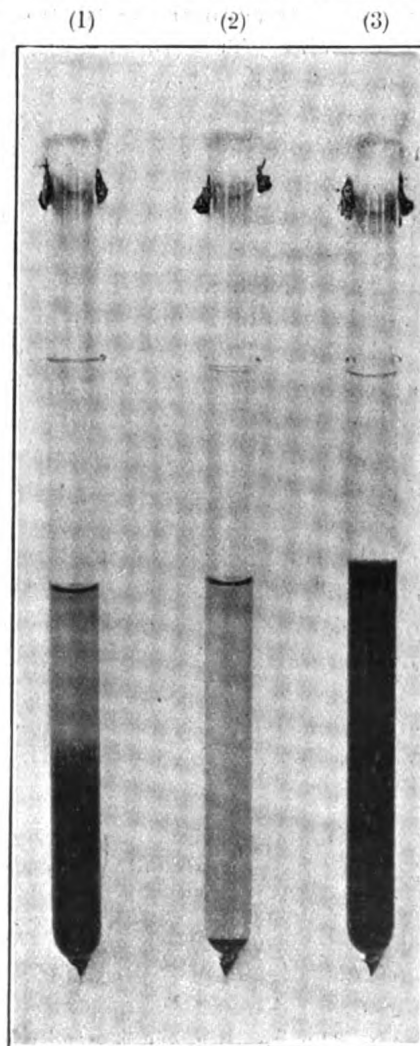


FIG. 2.

- (1) Cerebrospinal fluid of general paralysis showing the Wassermann reaction on removal from the incubator.
- (2) Ditto, after standing overnight on ice.
- (3) Control with normal cerebrospinal fluid, showing total hæmolysis.

added and the total volume made up to 2 cc. with saline solution. The series of tubes containing these mixed solutions are placed in an incubator at 37° C. for one hour, and then the sensitised blood corpuscles are added. (By sensitised corpuscles I mean washed sheep's corpuscles in immune rabbit's serum which has been heated.) The mixtures are again placed in the incubator for two hours at 37° C., then taken out and put on ice over night. The next morning the amount of hæmolysis in each tube is estimated (*vide* Fig. 2). If, on the one hand, antigen and antibody have been present they have united with the complement, and no solution of corpuscles will have taken place because the complement is fixed; if, on the other hand, the immune body (antibody) was not present then the complement (cytase) has remained free to act upon the sensitised corpuscles and lead to their solution. A control experiment, using a normal serum, or cerebrospinal fluid, viz., one which contains no antibody, must be used at the same time.

In the hands of nearly all trustworthy and experienced investigators this method introduced by Wassermann has yielded most valuable results as a means of diagnosis. It is claimed even that it is more reliable than the Widal reaction for typhoid. Plaut obtained a positive reaction in 80 to 90 per cent. of undoubted cases of syphilis by this method. He found the reaction specific; it is not definitely present in a non-syphilitic individual; it enables a diagnosis of the constitutional disease to be made but not of the organ affected. He did not obtain the reaction with the cerebrospinal fluid in 25 cases of syphilis in which the nervous system was not affected, while the serum as a rule gave a positive reaction. This was not to be expected from what has already been said as regards the cerebrospinal fluid and its secretion. It shows that the reaction depends upon the production of some substances by the tissues of the nervous system themselves. The nature and origin of that substance will be discussed a little later, but reference will now be made to the remarkable unanimity of opinion of all those who have made experiments upon this subject as to the almost certainty with which the cerebrospinal fluid of general paralytics and, to a less degree, tabetics give this Wassermann reaction. According to Plaut the reaction may be negative with the cerebrospinal fluid in cases of syphilis of the nervous system, but he obtained a positive result in 94 out of 95 cases of general paralysis with the cerebrospinal fluid, and in every one of the cases the serum gave a positive reaction. In cases of cerebral syphilis the serum was usually positive and the cerebrospinal fluid usually negative; in 70 to 80 per cent. of the cases of tabes the cerebrospinal fluid gave a positive reaction. Citron, G. Meier, W. Fischer and G. Meier, Michaelis, Weygandt, Fleischmann and W. J. Butler and others have obtained similar positive results by

this method. At my suggestion, my assistant, Dr. Candler, in conjunction with Dr. Henderson Smith, of the Lister Institute of Preventive Medicine, has been engaged in applying this reaction to a number of my cases in the hospital and the asylums, with the following results:—

They have now examined the cerebrospinal fluid of 100 cases, of which 94 were asylum cases and six were in general hospitals. Forty-six cases of general paralysis were examined, 41 of which gave a positive reaction by the Wassermann test, a percentage of 89·1. The reaction was not obtained in any of the control cases. Two cases of locomotor ataxia failed to give the reaction, but it may be noted that neither was in an active stage. A negative reaction was also obtained in a case of syphilitic meningitis in which the cell contents of the cerebrospinal fluid were diminishing rapidly in numbers under specific treatment. It is also interesting to note that cases of tubercular meningitis failed to give the reaction, although in one case the cerebrospinal fluid contained a large number of leucocytes per cubic millimetre (*vide* Table).

AN ANALYSIS OF THE RESULTS OF THE WASSERMANN-PLAUT  
REACTION ON THE CEREBRO-SPINAL FLUID OF 100 CASES.

TABLE I.—SHOWING THE RESULTS OF 94 ASYLUM CASES.

	No. of Cases.	Wassermann. +	Wassermann. —	Percentage of + reaction.	No. of cases confirmed by autopsy.
Total number of cases of—					
General Paralysis, examined during life ...	42*	37	5	88·9 %	4†
(?) " " " " " " ...	6	—	6	—	—
Non-General paralysis " " " " ...	16	—	16	—	—
Locomotor ataxia " " " " ...	2	—	2	—	—
Insanity, examined during life (by lumbar puncture) ...	66	—	—	—	—
General paralysis (post mortem) ...	4	4	—	100 %	—
Non-General " " " " ...	24	—	23, 1 doubtful	—	—
Total number of cases examined—					
Post mortem ...	28	—	—	—	—
During life and post mortem ...	94	—	—	—	—
Total number of cases of general paralysis, examined during life and post mortem ...	46	41	5	89·1 %	—

\* In six of the above 42 cases of G.P.I., the serum obtained from the blood, withdrawn during life, gave a positive Wassermann reaction.

† The C.S.F. of the four cases examined (post mortem), gave a similar result with the Wassermann Test as during life.

TABLE II.—SHOWING THE RESULTS OF 6 CONTROL HOSPITAL CASES.

No.	Institution	Nature of Case.	Wassermann reaction.
1	Charing Cross Hospital...	Tubercular Meningitis. (P. M.)	—
2	" " "	Cerebellar tumour (totally blind.) (P. M.)	—
3	" " "	Syphilitic meningitis— 1st examination, cell count 70 per 1 c.m. 2nd " " " " 20 "	—
4	Victoria Hospital for Children	Tubercular meningitis	—
5	" " "	" "	—
6	Charing Cross Hospital...	" "	—
(1 c.m.=100 leucocytes, 8 % lymphocytes).			—

I wish here to acknowledge the kind assistance which has been rendered during this research by Dr. Robert Jones, the Medical Superintendent, and Dr. Hughes, Medical Officer of the London County Asylum at Claybury; Dr. Bond, the Medical Superintendent of Long Grove Asylum; Dr. Ingram and other medical officers of the London Infirmary; Mr. Gibbs, Surgeon at the London Lock Hospital; and Dr. Nepean Longridge, of Queen Charlotte's Lying-in Hospital for Women.

For the purpose of diagnosis, therefore, especially of general paralysis (Fig. 2), it is a very important addition to clinical methods. Since its application, however, many doubts have been cast upon the interpretation of the facts whether indeed the reaction is in any way due to syphilitic antibodies.

Levaditi and Yamanouchi made a study of the diagnosis of syphilis and general paralysis by the Wassermann method. The results of their researches are very favourable from the clinical diagnostic point of view. Levaditi and Marie have demonstrated the facts that normal liver can replace the syphilitic liver in the preparation of the antigen, and the cerebrospinal fluid of general paralytics supposed to be rich in antibodies is devoid of spirillicide properties. These facts show that the sero-reaction in question, although clinically a specific test for syphilis, had nothing to do with syphilitic antigens and antibodies. Moreover, the active substances of liver extract, syphilitic or normal, contrary to the true antigens, are soluble in alcohol; and the sero-reaction can be obtained with bile salts and with lecithin, or with soap (Sachs and Altmann), cholesterine and vaselin (Fleischmann), although more feebly. The sero-reaction of syphilis and of general paralysis is the same, and is not due to the intervention of antibody or syphilitic antigen in the usual sense of the word, and has no relation with the *Spirochaeta pallida*. Landsteiner and Porges have also demonstrated that the extract of the liver

owes its particular properties for this reaction to the presence of lipoids and bile salts soluble in alcohol at 80° C. These products are found not only in the liver but also in different organs of man and animals. Landsteiner, Müller and Potzl state that in syphilitic serum substances are present which in the general sense are not anti-syphilitic bodies but which bind up with certain constituents of normal and syphilitic tissues. Moreover, they assert that the blood serum of animals infected with *Tryp. equiperdum* and *Tryp. Gambiense* contain similar substances which they have called *histaffnes*. Yet being a characteristic reaction, it is attributable to the presence in the serum and in the cerebrospinal fluid of certain at present unknown compounds, which in the presence of bile salts, soaps and lipoids of the liver precipitate and determine the fixation of the complement. Levaditi and Yamanouchi consider that these compounds arising in the organism itself may be a cholesterin ester. Thus it will be seen that these authorities give a new interpretation to the phenomena of the Wassermann method, which, however, in no way militates against its value as a practical method of diagnosis.

They also assert that there are between normal serums and lipoids of the body and specific serums and liquids, only quantitative and not qualitative differences; the reaction of Wassermann is provoked by histogenic and not bacterial substances. They find, moreover, that lipoids serving for sero-diagnosis not only exist in the liver but in other organs, the brain, the corpuscles of the blood, etc. They are probably complexes in which lecithin largely enters into the composition.

Levaditi, Ravaut and Yamanouchi have proved that when syphilis leaves intact the central nervous system, although the serum gives a positive reaction the cerebrospinal fluid does not, and this is what one would expect. It is, however, different when the central nervous system is affected even in a slight degree. The cerebrospinal fluid can then acquire properties which enable it to yield the Wassermann reaction. In fact, in the four cases out of the many examined presenting nervous symptoms, which were neither tabetics nor paralytics, the fluid has twice given a positive reaction, although quite feeble. The method of fixation of the complement would up to a certain point then serve for the early diagnosis of syphilis, especially when the brain is affected.

The researches of the above-named authors show that there is not any parallelism between the results furnished by the cytological examination and those obtained by the Wassermann method. The leucocyte reaction may be very marked in certain secondary specific cases without the cerebrospinal fluid being in the least able to fix the complement. Such was the case in one of my patients with well-marked syphilitic cerebrospinal meningitis. This patient was a woman, aged 34 years,



admitted, under my care at Charing Cross Hospital, as a case of tabes. Upon examination I diagnosed cerebrospinal syphilitic meningitis (pseudo-tabes). Lumbar puncture was performed, and the fluid was found to contain 370 lymphocytes per cubic millimetre; she was put on mercurial inunction, and in a fortnight she had greatly improved. The lymphocytes were now only 70 per cubic millimetre; a fortnight later the lymphocyte count was 20 per cubic millimetre, and she was well enough to be discharged, nearly all the symptoms having disappeared. The Wassermann reaction was negative on the last two occasions, when lumbar puncture was performed; it was not tried in the first instance. The existence of numbers of lymphocytes in the spinal canal does not necessarily entail the appearance of substances which in the presence of lipoids engender the phenomenon of Wassermann. Marie and Levaditi found that there is a parallelism between the rapidity of progress of general paralysis and the degree of intensity of the Wassermann reaction, with which observations the results of Drs. Henderson Smith and Candler are in agreement; no doubt, therefore, there is a connection between the breaking down of nervous substances (destructive metabolism) and the amount of this complex lipid substance, with which probably the reaction is associated and upon which it in a measure depends. I have been attempting to ascertain the chemical nature of this substance but my results are not yet sufficiently advanced to make any definite statement. However, I have found that the blood and cerebrospinal fluid in parasyphilitic affections contain a marked excess of lipoids, inorganic salts and splitting products of the phosphatides; and that this excess is proportional to the intensity of the disease. I have also found that a cerebrospinal fluid which gives a positive Wassermann reaction, after removal of the protein content by precipitation with alcohol, fails to give the reaction. I am therefore in agreement with Noguchi who, working on the relation of protein, lipoids and salts to the Wassermann reaction, has come to the following conclusions:—

1. The high value in respect to complement-binding exhibited by blood sera from syphilitics and spinal fluids from general paralytics is associated with an excessively high content of globulin, but there does not exist a direct quantitative relation between the two. Cases of secondary syphilis which have been under prolonged and proper medication do not exhibit the globulin increase, and usually fail to give the Wassermann reaction. The active substances entering into the Wassermann reaction are precipitable with the globulin, and chiefly with the euglobulin fraction of the fluids.

2. Temperatures of 70° to 76° C. destroy the active substances. Exposed to sunlight, the active substances deteriorate slowly. A photodynamic substance such as eosin, under the direct influence of the sun, brings about their complete and rapid

destruction. This effect does not occur in the dark. The active substances are subject to tryptic and peptic digestion, and are destroyed by weak acids and alkalies.

3. The active substances in the blood sera and spinal fluids cannot be separated from them or from the globulin precipitate by alcohol.

4. There are contained in the alcoholic extracts of normal and syphilitic blood and organs certain acetone-soluble lipoids which possess high antigenic values for the Wassermann reaction. Cholesterin is inactive, and the bile salts less active than the lipoidal bodies.

5. Sodium cholate is about as active as sodium taurocholate, but neurin and cholin are inactive.

Porges and Meier found that by addition of lecithin certain substances contained in syphilitic serum are rendered evident by a flocculent precipitate, and they have employed this method in place of the deviation of the complement method. But it is generally thought that this precipitation method is not so specific as the Wassermann method; moreover, Neubauer, Porges and Salomon were able to show that syphilitic serum only behaves stronger in this respect than normal serum. Fritz and Kren found that the lecithin test is not absolutely reliable, for non-specific diseases as tuberculosis, lepra, etc., give a precipitation; still less reliable is the test with glycocholate and taurocholate of soda. In respect to the Klausner reaction of globulin precipitation it was found that it was more uncertain than the lecithin and bile salts flocculation.

Neisser, Brück and Stern's investigations are of importance, for they have made a large number of experiments with apes and anthropoid apes, as well as observations on human beings. They conclude that the antigens are not identical with the living virus, nor of the same substance. They do not consider that mercury and atoxyl cause a destruction of the antigen but that treatment by these drugs injures or destroys the spirochaetes. Moreover, it has been found that antibodies exist normally in small quantities in some of the lower apes; it has so far not been found in the higher apes; it is therefore not a new product in syphilis but it is enormously increased in quantity in this disease. They consider that the serum diagnosis researches prove a direct association of syphilis, tabes and general paralysis. Immunity to reinoculation occurs when the virus has become generalised in the blood and lymph (Neisser). It is probable that the generalisation of the virus engenders simultaneously changes in the properties of the serum by which changes it becomes capable of giving the Wassermann reaction and preventing re-inoculation.

There are a number of other reactions which show that a profound bio-chemical change occurs in the blood in constitutional syphilis. Thus Klausner has shown that distilled water added to syphilitic serum causes a precipitation due to the amount of a precipitable globulin which syphilitic

serum contains. Fornet and Schereschewsky have shown that the serum of paralytics and tabetics exclusively give with the serum of syphilitic patients a positive precipitin reaction. It is claimed, therefore, by them that this observation proves the syphilogenous origin of these two diseases.

The simpler method of Noguchi, to which I have been giving attention, consists in boiling two parts of the cerebrospinal fluid with five parts of a 10 per cent. solution of butyric acid in saline solution for a few seconds and then adding one part of normal NaOH solution and again boiling briefly. A flocculent precipitate is obtained in parasymphilitic affections. It is due to the presence of a globulin; it has before been remarked that there is a parallelism between the presence of albumin in cerebrospinal fluid and the Wassermann reaction.

*Summary.*—The original method of Wassermann is the most complicated, but is regarded by the majority of investigators as the most specific and reliable. Whatever may be the explanation of the facts all the evidence goes to prove: (1) That these methods in the hands of competent observers afford a valuable means of diagnosis and are especially useful when applied to the cerebrospinal fluid for the determination of the existence or not of general paralysis. (2) That similar substances, whether antibodies or not, occur in the serum of syphilitic and parasymphilitic persons in such quantities as are not found in the serum of normal persons or in the sera of people suffering with other diseases. (3) That similar substances are found in the cerebrospinal fluid of tabetics and general paralytics, and the amount of those substances which cause a deviation of the complement or a precipitation is in proportion to the activity and length of duration of the disease; that these substances are of tissue origin or arise from tissue destruction caused in some way by the action present or past of the syphilitic virus. (4) It is probable that the syphilitic virus excites an increased unloosening of complex lipoid substances containing lecithin and cholesterolin, etc., from the red corpuscles and cells of the body. (5) That this prevails through life, and in certain cases of syphilitic infection, viz., general paralysis and tabes, the central nervous system, which under ordinary circumstances is protected against the loss of its lipoid substances, takes part in the process, and this is manifested by the presence of lipoids and globulins in the cerebrospinal fluid, and these act as antibodies in the reaction. This lipoid complex, as well as globulin, increases in amount as the process of neuronie decay proceeds. It is probably owing to the presence of these substances that the granulation of the ventricles, so characteristic a feature of general paralysis, arises as a result of stimulation to proliferative hyperplasia of the ependymal epithelium. Choline may also be present owing to decomposition of

lecithin, but this may occur in any active degenerative process of the myelin, and is not pathognomonic of any particular disease.

Other lipoids of the phosphatide group are present usually in considerable amount and in proportion to the extent of myelin destruction and dissociation. I have pointed this out in the Archives of Neurology, Vol. II., 1902, p. 304, when after referring to the work of Flexner, Noguchi and Kyes on cobra venom I stated that:—

The products of degeneration of nervous tissues are numerous, and consist not only of choline, but also of a number of bodies of the lecithin group, being various derivations of "protagon." Choline is the most easily separated and recognised physiologically and chemically, and it is possible that the products of degeneration vary according to the cause and nature of the destructive process. Still, there is no evidence to show that these products of degeneration can *per se* produce the clinical manifestations and morphological changes indicating neuronc irritation and destruction of general paralysis, otherwise we ought to get these changes in other diseases, also destructive lesions of the nervous system. Therefore, I think it may be conceived as possible that there is a latent toxin in the blood which combines with endo-complements the products of deranged neuron activity, producing locally (this is, where the neuron metabolism is deranged either by stress, circulatory deficiencies, or hereditary, physiological, or anatomical defects) an active neurolysin proportional to (a) the amount of latent toxin in the blood; and (b) the amount of endo-complement produced by the deranged neuron metabolism.

Blumenthal states that he has found that the blood of syphilitic persons, also of tabetics and paralytics, contains a large increase of lecithin as compared with the normal. He finds also an increase of lecithin in the fæces in tabes and general paralysis and a great decrease in the bone marrow. He considers that tabes and paralysis are associated with a progressive impoverishment of the body in lecithin. It is more probable that there is an impoverishment of lipoids, including the important substance, cholesterolin.

### LECTURE III.

I endeavoured in my last lectures to indicate some of the advances made in our knowledge of the biology and bio-chemistry of syphilis, and in my final lecture I will try to correlate the facts with clinico-anatomical knowledge, especially in relation to the etiology of the parasymphilitic affections, tabes, and general paralysis.

#### PARASYPHILIS (FOURNIER): METASYPHILIS (MOEBIUS).

Parasyphilis is the term given by Fournier to those diseases of which syphilis is essentially the cause, but which are not directly the result of the syphilitic virus. Such diseases are: general paralysis, tabes dorsalis, tabo-paralysis and primary optic atrophy. These diseases

are really a single morbid entity owning the same cause; insidious in onset, progressive in character, and uninfluenced by anti-syphilitic remedies. These various clinical types of parasymphilitic disease are the result of a primary neuronc dystrophy; they have a similar pathogenesis and may occur simultaneously or successively in the same individual. In *tabes dorsalis* the spinal sensory protoneurons are affected; in general paralysis the cortical association neurons; in *tabo-paralysis* both are affected simultaneously or successively. The dystrophic process is due to a lack of durability of the neurons; it may be a slow process of decay and death of the intra-spinal portion of the sensory protoneurons, as in the case of *tabes dorsalis*; it may be a rapid process of decay and death of systems and communities of neurons of the brain, as in general paralysis. The former is a smouldering destruction of neural elements, the latter a conflagration often fanned into flames by microbial toxæmia, autotoxæmia, or circulatory disturbances associated with arterial anæmia and venous congestion with blood stasis of the brain. It is probable that Erb's spinal paralysis and certain cases of amyotrophic lateral sclerosis may be primary post-symphilitic dystrophies.

Fournier thus classifies parasymphilitic affections:—

#### I. ACQUIRED SYPHILIS.

1. Acute hystero-neurasthenia of the secondary period.
2. Different neurasthenic manifestations of a more advanced stage.
3. *Tabes*.
4. General paralysis.
5. A special form of epilepsy.
6. A special form of muscular atrophy.

#### II. HEREDO-SYPHILIS.

Numerous dystrophic troubles, general or partial; malformation, notably dental; arrest or retardation of physical and intellectual development, infantilism, dwarfism, inborn lack of vitality, cachexia, marasmus, rickets, hydrocephalus, certain forms of simple meningitis in early life, possibly certain cases of true epilepsy, juvenile *tabes*, spinal and optic juvenile general paresis. The gravity of these affections lies in the fact that they are uninfluenced by antisymphilitic treatment. The local and general failure of development may be due (1) to the direct influence of the virus upon the life and growth of the tissues, or (2) indirectly to exhaustion of the specific energy of the cells of the central nervous system by the establishment of an altered metabolism, the bio-chemical

nature of which is not yet fully understood. But, as a provisional hypothesis, we might suggest that the unloosening of lipoid substances into the blood, which we know occurs in congenital syphilis, may lead to a defective *vita propria* of all the cells of the body. In some lesions of congenital syphilis it may be actually due to the local invasions and multiplication of the spirochaete, for they have been found in abundance in situations where local lesions exist, *e.g.*, the epiphysis of bone, and why not in the epiblastic enamel germs.

We might provisionally suggest as a hypothesis that in all cases of acquired and congenital syphilis the living contagium (spirochaete) excites the tissues and fluids of the body to a defensive reaction. The difference in the effects of inoculation may depend upon the virus itself. Some striking examples will be given (p. 50) which apparently indicate that there may be a special neurotoxic virus, and if such instances were more numerous we could hardly believe that coincidence could explain the facts. If, as there is reason to believe, the *Spirochaeta Pallida* is the living contagium, and that, becoming generalised in the lymph and blood stream, it produces the secondary manifestations, then there is a certain amount of chance what tissues will be attacked; for the living agent, swept along in the blood stream, may become lodged anywhere, and, by blocking capillaries, cause a local focus of tissue infection. The existence of a generalised eruption implies virulence of the circulating blood, and experiments demonstrate the fact that the blood is virulent during the eruptive stage; thus, Neisser has obtained a positive result by injection of blood into the skin in the chimpanzee, and Roux and Metchnikoff have successfully inoculated a Macaque monkey from the blood of a chimpanzee in the eruptive period. It would be of great interest to know how long the virulence of the blood persists after the generalised eruption, or if the consecutive attacks which may occur even after 15 or 20 years are explained by the "contagium vivum" remaining latent in the lymphatic glands or some deep-seated organ. What is the evidence in favour of this view? It is generally admitted that the subjects of tabes and general paralysis are recruited especially from those individuals who have had a mild attack and who very seldom show any signs or symptoms of tertiary gummatous skin, visceral or bone lesions. Fournier states: "The comparative mildness of the primary constitutional symptoms in those who ultimately become tabetic would almost seem to indicate that, when the syphilitic virus expends itself in severe primary and secondary manifestations, there is a less tendency to the subtle poison which proves so disastrous to the nervous system." From an experience of over 500 *post-mortems* made on paralytic patients, I have been surprised at the rarity of severe tertiary skin and visceral

lesions as compared with the cases of true syphilitic brain disease. Arterio-sclerosis, in the form of fibrotic plaques of the aorta, is, however, very common in paralytic dementia, which, however, is now regarded as a parasyphilitic affection. Again, although paralytics in the prodromal stages of the disease often give themselves up to debauchery and sexual congress with loose women, I have never seen or had my attention called to a case of general paralysis among the vast numbers in the London County Asylums that showed a primary sore or a secondary rash. Krafft-Ebing noted the same fact, and concluded that the reason was that every paralytic had had syphilis and was therefore immune. He caused this hypothesis to be put to a crucial test. Nine cases of general paralysis were selected that gave no history and showed no signs on the body; these patients were inoculated with the virus of a typical hard chancre and watched for 180 days. They presented no signs of infection. The only assumption is that they were immune owing to previous infection, and that they possessed a power of resisting the action of the syphilitic virus. The concordance of this result with the statistical data of antecedent, inherited, or acquired syphilis in cases of tabes and general paralysis given later, led to the widespread acceptance by neurologists of the view that tabes spinalis or cerebialis (general paralysis) is essentially of syphilitic origin. No syphilis, no tabes. Only a few eminent neurologists, such as Von Leyden, refuse to accept the syphilitic origin of tabes, and one of the arguments employed against this view is that anti-syphilitic remedies are of no avail in preventing the disease or arresting its progress. Moreover, we know that many people develop general paralysis or tabes dorsalis, even though they have been treated with mercury systematically from the primary infection onwards. So much has this impressed some authorities that they have even asserted that over-mercurialisation is the cause of the disease in question. The average time which elapses between the primary sore and the onset of tabes and general paralysis is, according to the observations of Schuster, the same in persons who have been thoroughly treated with mercury and those who have either not been treated at all, or only insufficiently. All the facts, therefore, go to prove that the syphilitic virus has in some way or other damaged the durability of the neurones, so that systems or communities die prematurely. It has been observed that Fournier includes other functional and organic diseases of the nervous system among the parasyphilitic affections. We have less knowledge concerning them and their pathogenesis. I have, however, seen cases of general paralysis in which the motor symptoms were most pronounced and the dementia slight, in which all the deep reflexes were exaggerated, and the plantar extensor reflex present on both sides—a very unusual occurrence in the

ordinary paralytic dementia. At the autopsies there was a well-marked sclerosis of the crossed pyramidal tracts without any coarse lesion in the brain and cord to account for it. I have also seen cases of progressive amyotrophic lateral sclerosis occurring in the subjects of syphilis which appeared to be the result of the progressive degeneration of the whole motor efferent tract from cortex to periphery without any sensory disturbance. Some of the cases of Raymond cited by Fournier with sensory troubles, viz., rheumatic pains and paræsthesiæ, are obviously, from the account given of the appearances of the spinal cord *post mortem*, cases of sub-acute gummatous meningitis involving the roots. The serum diagnosis and the examination of the cerebrospinal fluid bio-chemically and microscopically will permit us in future to determine whether syphilis is the essential cause of these degenerations. For every nervous disease, whether functional or organic, occurring in a person who has suffered from syphilis is not necessarily syphilitic in origin, yet, when we consider the profound influence the virus has upon the blood and tissues of the whole body, it is not illogical to assume that any disease, local or constitutional, functional or organic, occurring in a person who has acquired or inherited syphilis may possibly have found a suitable soil for development, owing to the diminished vital resistance of the tissues, occasioned by such a potent and persistent poison as syphilis. Thus syphilis, although not a direct agent in such a case, by its devitalising influence and the impoverishment of the lipoids, becomes an important indirect causal factor of the disease in question. There are many known ways in which syphilis can cause functional disturbances of the nervous system and lead to the development of neuroses and psychoses. The theory of the possibility of the syphilitic virus, or the lipid products of its activity, stimulating the neurons to increased dissimilative action and exhaustion has been shown to have considerable support from recent investigations. (*Vide* p. 40.) There are, however, other conditions which are well known, viz., the change in the blood and blood vessels, and in the lymph and lymph channels. Long ago, Virchow pointed out that in syphilis there is a diminution of red blood corpuscles and a hyperalbuminosis. Later, Schulgowski, Hafter and Laacke described a considerable fall in the red blood corpuscle count. In the secondary stage Martin and Hiller, also Letzius, showed that not only is there a diminution in the number of red blood corpuscles, but also an absolute diminution of the hæmoglobin content of the corpuscle. Anz found, besides the fall in number of the red blood corpuscles, an increase of the white, so that one can speak of a relative and absolute leucocytosis. Later observers showed that there was a diminution of polynuclear leucocytes, and that the



leucocytosis was due to a great increase of lymphocytes, which increase we may associate with the polyadenitis. Further, there is an increase of eosinophils. These changes in the blood in the secondary period increase in intensity with each fresh series of syphilitic manifestations, and diminish as they diminish; moreover, the blood changes disappear with the disappearance of the secondary symptoms under anti-syphilitic treatment. Fournier long ago described the favourable influence of mercury upon the blood formation; clearly, then, the mercury, by its influence upon the productiveness of the syphilitic virus, allows a return of the normal hæmapoietic formation, or arrests a too rapid hæmolytic action. The French authorities were the first to call attention to a syphilitic anæmia, and to point out that iron had no influence thereon. The ebb and flow of the amount of oxyhæmoglobin is correlative to the flow and ebb of lymphocytes, which might indicate that, with the pouring out of an abundance of lymphocytes from the lymph stream into the blood stream, there was associated a pouring out of the virus that occasioned the irritation and hyperplasia of the lymph-cell elements. Hoffmann asserts that he has observed the serum of a syphilitic patient produce immobility and agglutination of the spirochaetes. Perchance it is that when the virus can no longer be neutralised by the defensive reaction of the blood serum embolic capillary effects are produced, causing papular eruptions of the skin, mucous tubercles, and occasionally, meningitis. Selenew demonstrated blood changes before the outbreak of the secondary exanthem, therefore before the secondary incubation stage. It is probable that before the eruption becomes visible, microscopic changes have occurred in the affected cutaneous capillaries and adjacent skin structures, much in the same way as in the primary sore; consequently, we should expect a blood change to precede the eruption. The anæmia may be due to a hæmolysis owing to an unloosening of lipid substances (lecithins and cholesterin) from the red corpuscles by the action of a toxic substance of the virus acting as a lipolytic ferment disintegrating the osmotic membranes or by chemical interaction in the lecithin and cholesterin complex, forming the osmotic membrane\* producing physical changes by which the membrane becomes permeable even to the large hæmoglobin molecules. (Fig. 1.) It may be supposed that the protein stroma of the corpuscle is covered by a film or membrane formed of this lipid substance, and the virus acts upon it in such a way as to dissolve, dissociate, or destroy the membranous film covering the corpuscle, and causing thereby a liberation of both the hæmoglobin and the

\* The idea of the existence of an osmotic membrane was first conceived by Prof. Schafer, as far as I know, in the description of the blood. (Quain's Anatomy, 1893.)

He gives many facts in support of his arguments in favour of the existence of such a membrane.

lipoid substances into the serum. According to Levaditi and Yamanouchi the lipoids serving for serum diagnosis not only exist in the liver but in other organs, the brain and the red corpuscles. They are probably complexes in which lecithin enters largely. The anæmia may, however, be due to interference with the functions of the hæmapoietic tissues; in support of this is the fact established experimentally by Neisser that the red marrow and spleen are especially rich in the virus. Since mercury can rapidly improve this blood dyscrasia, it is probable that it does so by arresting the development of the *contagium vivum* in these blood-forming tissues. In congenital syphilitic children hæmoglobinuria may occur, and this may be due to the existence of a large quantity of the virus in the blood causing hæmolysis of the corpuscles. Many authorities working at the subject of metabolism in syphilis have shown that the nitrogen metabolism is altered. "Von Boick, Stephanow, and Bjelakow found that the assimilation of nitrogen of food sinks, and the percentage of extractives increases considerably in relation to the urea." (Max Nonne.) This would indicate an altered dissimilative metabolism. There is, therefore, considerable evidence to show that causes exist which render the organs of the body more vulnerable, not only to other infective agencies, *e.g.*, tubercle causing scrofula, but also to the evolution and development of neuroses and degenerations by a devitalising influence on the tissues by the unloosening of lipoid substances. We have now to consider how far do these researches, biological and biochemical, help us in determining the etiology of tabes and general paralysis.

#### ETIOLOGY OF TABES.

(*Tabes Dorsalis, Tabes Optica, Tabo-Paralysis, General Paralysis*)

The Wassermann method of diagnosis has come to strengthen and confirm the belief of many neurologists like myself: "*no syphilis, no tabes*;" this was previously based solely upon statistics and observations relating to the etiology of the disease. Moreover, the etiology and the serum diagnosis are reciprocally supporting not only of the parasymphilitic theory, but also of the view that there is one morbid entity which may be described as tabes; a view first put forward by Fournier, and which I have supported by comparing the clinical notes, and in a large number of instances the *post-mortem* results (with microscopic investigation) of sixty cases of tabes dorsalis and sixty cases of tabo-paralysis. I came to the conclusion that Fournier was justified in asserting the identical relation of the etiology, the close relationship and overlapping in the symptomatology and pathology, and that he was right when he destined them one day or other to be grouped in a single pathological entity; for

Ferrier, in his admirable Lumleian Lectures on *tabes dorsalis*, says: ". . . and here I would express in concurrence with Fournier, Mott, and many other neuro-pathologists of the present day, my belief in the essential pathological identity of *tabes* and general paralysis. They are, in my opinion, merely different aspects of the same polymorphic disease." Both are tabetic, or wasting, affections of the sensory proton-eurons in the one case and of the cortical neurons in the other. The essential etiological factor is the same, and the average time elapsing between the primary infection and the onset of the degenerative process corresponds in the two diseases. Fournier remarks that the establishment of the syphilitic origin of *tabes dorsalis*, from his experience, would necessarily end in the application of the doctrine to general paralysis. In fact, there are so many symptoms in common and so many analogies of evolution and termination associating these two diseases that it was quite natural to conclude the etiology of one from that of the other.

I have endeavoured to show in the Archives of Neurology, Vols. I. and II., and elsewhere, all the evidence of the etiology of *tabes* and general paralysis tends to prove that there is in all probability one essential cause, syphilis, acquired or congenital, and that there are a number of contributing factors, any one of which by itself or even in combination with others, *e.g.*, sexual excess, mental stress, heredity, injury, alcohol, is not capable of producing the disease. The fact that congenital syphilis leads both to *tabes* and general paralysis at so early a period of life as to exclude most of the contributory factors except heredity, is an argument in favour of syphilis being the essential cause. Moreover, males and females are affected with juvenile optic *tabes*, *tabes* and general paralysis, in equal numbers. Thus, of 500 general paralytics that have died and been examined *post mortem* at Claybury, there were 5 males and 5 females who suffered with juvenile general paralysis; that is, 2 per cent. of the total. I may here remark that this condition was first described by Dr. Clouston. The study of heredo-syphilis in relation to these parasymphilitic affections is especially convincing as to the essential cause of *tabes* and general paralysis being syphilis. This has been brought home to me in a very convincing manner in the large number of cases in which I have studied the family histories. I will cite a few examples: A young man was admitted to Claybury suffering with what were termed epileptic fits, the seizures did not cease, and he died; externally there was nothing on his body to show that he had congenital syphilis; his liver, however, showed typical signs of congenital syphilis, and the brain was typical of general paralysis. A brother in Caterham Asylum presented the facies of a typical congenital syphilitic. I ascertained that the father died of general paralysis, and the

mother, when I interviewed her, was in the early stage of dementia. I was asked to see recently at Hanwell a young girl who, blind from optic atrophy, had later become demented. I was informed there were no signs of syphilis on the body, and she was one of a large grown-up family. Fortunately the mother was there at the time. I therefore had the opportunity of interrogating her. I found it was quite correct that she was one of a large family, but I also ascertained that, prior to the birth of this child, there had been several miscarriages and still-born children, that this child had suffered with snuffles and a rash, that she had taken it to the hospital, and grey powders had been given. When the rash disappeared, she ceased to attend further. As so often happens in these cases, the mother had not apparently suffered, and showed no signs of syphilis. Another example I may mention: A juvenile paralytic boy was admitted to Bexley and died there; recently his brother has been admitted with commencing signs of the disease. The former had Hutchinson teeth, but no history of syphilis could be obtained from the father. This man died in Guy's Hospital. I wrote to the registrar, and I received the information that he had had syphilis. Perhaps the most convincing case is the following one, which died in Claybury about a year ago: A boy was admitted with dementia, contraction of all four limbs, and epileptic seizures; dying not long after admission, the *post-mortem* examination revealed very advanced general paralysis. There were no signs on the body, and the boy, up to twelve years of age, was bright and intelligent; then mental symptoms set in and steadily progressed. A history from the father showed that five years before marriage he had contracted syphilis, which, in spite of long treatment by an eminent physician, had not been cured, for the first child died within 48 hours of birth, the second within 24 hours, the third suffered with late interstitial keratitis, and later nerve-deafness; then came the patient, and afterwards healthy children. I could multiply these instances, for, altogether, I have notes of some 60 consecutive cases, and in the great majority (over 80 per cent.) there are indubitable signs, or an unquestionable history, as in the above cases, pointing to hereditary syphilis. I have found no case in which I could *certainly* exclude syphilis. Particularly common is optic atrophy, which takes these children to the blind school, and there they develop fits or signs of mental deterioration, and are next sent to the asylum.

The cases of tabes occurring in heredo-syphilis are not nearly so numerous as the cases of general paralysis; the ataxy is usually not very marked, optic atrophy is very common, and tabo-paralysis is met with often associated with optic atrophy; optic atrophy occurs also pretty frequently in the paralytic dementia of congenital syphilis. I have seen

two brothers so affected, and die after developing the signs of progressive dementia. The period of time elapsing between the evolution of tabes and general paralysis and the acquired infection varies considerably; it may be from 3 to 31 years; but the average is 8 to 15 years. The life of the neurons has been reduced, and the time that will elapse between infection and the onset of decay depends upon the intensity of the virus and the inborn resistance of the nervous system, together with other supplemental factors causing stress. In these hereditary cases it is surprising how frequently we find one of the parents, and occasionally both, suffering from paralysis or tabes; this implies an inborn tendency to this degenerative condition. Now it may be asked if twenty-five years, or even more, can elapse in an adult between the acquirement of syphilis and the onset of the symptoms of parasyphilis, why should not the same long period occur occasionally in congenital syphilitic cases, so that instead of the first symptoms commencing at puberty they are not manifest till adolescence, or even considerably later. Nonne relates a case of a workman, aged 32, who had suffered for two years with lightning pains, and had never been infected with syphilis or addicted to drink, and who presented all the typical signs of ataxy. He had been treated in the hospital for severe hereditary syphilis. I have occasionally observed similar cases of general paralysis, *e.g.*: a man aged 28 died recently in one of the London County Asylums of very advanced general paralysis. The disease was first manifested at the age of 18, when he had a fit. His character was strange; he married, had one child born dead, and afterwards his wife left him. He had no signs of syphilis on his body, but I found that his father had died eight years previously in Claybury Asylum. In my Croonian Lectures upon the "Degeneration of the Neuron" I remarked that it is very probable that some of the cases occurring in adults in which syphilis can with certainty be excluded, may still owe the disease to an inherited syphilitic taint. It is not even necessary, as quite one-half of the juvenile cases show, that they should exhibit any external signs of congenital syphilis, for many of the juvenile cases which I collected were proved beyond doubt to be born of syphilitic parents, although manifesting themselves no external signs of syphilis, whereas brothers and sisters exhibited very definite signs. A case of general paralysis died at Banstead Asylum which had previously been under the care of Dr. Percy Smith at Bethlehem Hospital. This woman had characteristic signs of congenital syphilis, but she did not manifest symptoms of progressive dementia till she was 30 years of age. The patient was an unmarried woman, and there was no reason to believe that she had acquired the disease. Recently Christian Muller has put forward the same hypothesis to explain those cases in

which no history of acquired syphilis can be obtained. He describes two cases of women (virgins) who were the subjects of well-marked signs of congenital syphilis, and who died of general paralysis at the ages of 42 and 43 years. The symptoms were not noticeable until a year or two before death.

Dr. Ferrier has in a masterly manner reviewed the evidence which points to syphilis being the essential cause of general paralysis and tabes, and, in conclusion, I cannot do better than quote him:—"One might multiply arguments in favour of the causal relation between syphilis and tabes, but they are unnecessary. For those above related, singly and collectively, leave, in my opinion, little room for doubt that tabes and general paralysis are in all cases of syphilitic origin, and that tabes, *per se*, is as much a proof of antecedent syphilis as a gumma of the skin."

Although syphilis is the essential cause, yet, as Fournier showed, tabes and general paralysis are not syphilitic, but an outcome of syphilis, and the riddle is still unsolved why only about 3 to 5 per cent. of the persons infected with syphilis should subsequently suffer with one of these degenerations of the nervous system termed parasymphilitic. But only 10 to 15 per cent. of persons suffering with diphtheria develop post-diphtheritic paralysis; these are usually cases in which the local infective process was mild and often unnoticed; in that respect, like parasymphilitic affections, which, more often than not, follow mild and even unrecognised primary infection and secondary symptoms. Is it because the virus is attenuated or modified, and, thereby, has acquired a special neurotoxic action, or is it because, in a small percentage of individuals, the cells of the body, *especially the cells of the nervous system*, react to the virus in a hypersensitive manner? As already indicated, there are facts which suggest the possibility of a certain form of virus with a neurotoxic action. Thus, Babinski remarks that it seems possible that a syphilitic virus may sometimes be endowed with a particular aptitude for attacking the nervous system; he reports the case of two students who were infected the same day by the same woman; both died fifteen years later of general paralysis; these students were, however, related. I have recently heard of two professional men, not related, who acquired syphilis about the same time from the same nurse; ten years later they developed general paralysis. Marie and Bernhard relate the instance of two men who were infected from the same source, and ten years later suffered with tabes. Erb narrates an instance of four patients infected by the same woman, who later became the subjects of either tabes or general paralysis, whilst a fifth, who had connection with the woman but was not infected, did not suffer with any disease later. Probably the most striking example supporting this theory of a special neuro-

toxic virus has been afforded by Brosius, who relates that seven glass-blowers suffered with chancre of the lip, and out of five who ten years later came under observation, four suffered with either tabes or general paralysis. If we accept the fact that a spirochaete is the specific causal agent of syphilis, it is conceivable that there may be varieties of this organism, as there are of the malarial parasite or trypanosome. Again, the organism may become attenuated or modified in its passage through the bodies of certain individuals, or it may be attenuated or modified by the action of mercury. It may thus happen that the virus may vary in different cases of infection. This, however, is speculation, and is not supported, but rather contraindicated so far by experiments on animals. For, although lower apes have the disease in a mild form when inoculated from the human being, yet the syphilitic virus of an infected *Macacus Rhesus*, when used to infect a chimpanzee, appears to have lost none of its original virulence; for the chimpanzee suffers as badly as if it had been infected direct from the human source of the virus. We are probably, therefore, on more certain ground in attributing the variation of the effects which will follow infection, not to the variation of the virus, but to the reaction of the individual himself; and we may represent this in the form of an equation:—

$$\text{Symptom complex } x = \frac{V}{R} = \frac{\text{virus.}}{\text{resistance.}}$$

If the virus  $V$  is constant,  $R$  resistance must vary. But  $R$  is made up of a number of factors, some of which we can ascertain, but it is generally impossible to decompose  $R$  into all its constituents. Roughly speaking, we may say that it is made up of what a man is born with, what has happened after birth, and what will happen in the future to resist the reaction of the specific virus, which in the majority of instances is of life-long duration. Most authorities agree that with the widespread syphilisation of a race for many generations, the disease tends to assume a milder form; the effects of the disease are not so severe, and a widespread tendency to an inherited immunity has been brought about. The conversion of a rural into an urban population has done much towards racial syphilisation and to the diffusion of a tendency to inherited immunity, and the begetting thus of a mild form of disease. But, whereas there are fewer cases of severe syphilis than formerly, there are more cases of tabes and general paralysis. The interesting description given by Col. Lamb of the syphilisation of the natives of Uganda shows how severely a race previously free from this disease suffers from malignant skin, bone, and visceral disease. He also points out that tabes is very rarely seen. If we consider some facts concerning congenital syphilis, we must come to the conclusion that immunity is pos-

sible; how, otherwise, can we explain the law of Profeta, viz., the non-syphilitic child of a syphilitic mother does not acquire syphilis from the syphilised mother who suckles it? Again the child may be syphilitic, and the mother shows no signs of syphilis, the mother does not acquire syphilis by suckling that syphilitic child, whereas a wet nurse does. In the former case the fœtus has acquired some antitoxin or something from the maternal blood, which has stimulated its own tissues to react against the virus; in the latter (Colles' Law) the mother has derived from the blood of the syphilised child an antitoxin or something (not the living contagium) which has stimulated her tissues to react against the virus so effectively that she cannot be infected. There is no reason to suppose that the germ cells do not participate in this reaction, seeing that every cell in the body is subjected to the sensitising influence of the chemical products of the virus by means of the blood and lymph. The experiments of Ehrlich have been quoted by Neisser as opposing the view of inherited immunity; on the other hand, Kōnrad's recent experiments on lyssa support it. The histories I obtained in a large number of cases of juvenile general paralysis and cases of congenital syphilitic nervous disease revealed the fact that the mother very frequently had miscarriages, abortions, and typically syphilitic children, without herself suffering at all, or presenting any signs of syphilis. In two instances the mother died of general paralysis; in a considerable number of instances the father died of this disease. As a general rule, the result of successive conceptions is as follows: miscarriages, abortions, dead children, children dying in infancy—often of meningitis or hydrocephalus, children who later in life suffer with nervous affections, *e.g.*, nerve deafness, paralytic dementia, optic atrophy, and tabes; and, finally, healthy children. Such a chain of circumstances would undoubtedly indicate that either the virus was becoming attenuated or the resistance to its action was increased. In any case, we have reason to suppose that the children who were born with a syphilitic rash would be immune to reinfection, also those who afterwards suffered with parasymphilis; Krafft Ebing's observation supports this premise. It is probably a question of the degree of immunity to reinfection that would obtain in the presumably healthy children that followed the diseased ones. But such a chain of events does not always occur, for sometimes children are born with signs of heredo-syphilis after the birth of several healthy children, also parasymphilitic children may be born after the birth of several healthy children. This may be explained by the fact that the specific virus has become active again in the mother, which inference is negatived in most instances by the fact that she herself may say that she has been in good health and no signs of the disease



can be discovered in her. Another explanation offers itself, and it is that the specific virus may have attacked one ovum and spared another. Levaditi has seen the spirochaete within an ovum. No two individuals, even of the same family, are born alike, because the germ-plasm out of which they were formed may be similar, but is not the same; one inherits ancestral tendencies which the other does not; and it may happen, therefore, that a child born later than the healthy children possesses less inborn resistance to the action of the virus; consequently, manifests congenital syphilis or, later, parasyphilis. How can we explain this process of decay of particular groups, systems, and communities of neurons? Why should we have optic atrophy in one individual, atrophy of the spinal portion of the sensory protoneurons in another, decay and atrophy of the cortical neurons in a third, and, in many instances, a decay and atrophy of the whole nervous system? We cannot suppose that it is caused by the random metastasis of the syphilitic organism in the membranes, or coats of the blood vessels, conveyed by the lymph or blood stream, as is probably the case in the true syphilitic lesions of the brain and spinal cord. Everything points against this, for, although parasyphilitic affections present the most varied signs and symptoms, there is one sign usually present which is, for all practical purposes, only met with in parasyphilis, viz., the Argyll-Robertson pupil. No coarse random lesion will explain the constancy of this phenomenon; moreover, this condition, although a sign of syphilitic infection, does not occur in true syphilitic brain disease. Spirochaetes have never been found in the cerebrospinal fluid or antigens. Antibodies are found proportional to the extent of neuronal decay in tabes and general paralysis.

I think all the facts are against the views of Lesser, Bosc, and others that these late manifestations of degeneration of the nervous system may be regarded as quaternary syphilis, a very late effect of the virus comparable with syphilitic orchitis, glossitis, and other sclerous lesions. According to this view, we should be compelled to consider the meningeal and perivascular infiltrations and the glia cell proliferation as the cause of the degeneration. But there are many reasons why we cannot accept this hypothesis. The view I take of the process is that parasyphilitic disease of the nervous system depends upon two factors, intrinsic, innate, and extrinsic, acquired—the soil and the seed; the vital resistance and the specificity of the virus,  $\frac{V}{R}$ .

All those conditions which may be inherited or acquired, and which tend to active metabolism of systems, communities, and groups of neurons functionally correlated, owing to those conditions of stress causing in one individual spinal neurasthenia, in another cerebral

neurasthenia, will, in conjunction with the effect of the syphilitic poison on the lipoids, cause the nerve-cells to exercise an abnormal metabolic activity.

Ehrlich points out that we cannot suppose that the cells of the body possess, *per se*, an executive defensive capacity to neutralise the noxious effects of all forms of organisms, and his work on hæmolysins shows that the hæmolysin for the corpuscles of a particular animal only occurs after incorporation of the molecules of those corpuscles. But we may suppose that there is an *inherent* aptitude for the cells of the body of certain individuals to adapt themselves readily to defence against the action of the syphilitic virus in a race that has been widely syphilised for generations; consequently, a larger number will have a mild form of the disease. Cases of tabes and general paralysis occasionally arise within three years of the primary sore; possibly this may be due to an inherent hypersensibility to react to the poison. Dr. Byrom Bramwell has recorded a remarkable case of tabes which came on ten months after infection; it would be interesting to investigate the family history and past personal history of these cases to ascertain whether or not it was a second infection.

The nerve-cells are perpetual elements incapable of regeneration, highly differentiated, and complex in structure and function; their centre of nutrition is the nucleus, and when decay sets in, the regressive process attacks first the fine twigs and branches of the tree, the dendrites and dendrons, and the rootlets; in fact, the process is an inversion of its growth and development. But what should cause this premature decay and lack of durability, for the specific energy of the whole of the neurons in the healthy body is sufficient to last until the vital spark dies out? We know the more prolonged duration of infectivity of the syphilitic virus as compared with other contagious diseases, also that one attack of syphilis confers immunity during the rest of the individual's life; moreover, the experiments of Krafft-Ebing are important to remember in this respect. The nerve-elements being perpetual and having acquired a habit of increased metabolic activity, will continue it during life, and will contribute to the excess of lipoids in the blood. When there is no longer metabolic equilibrium, and decay sets in, these lipoid complexes are thrown off in increasing numbers (*vide* p. 37); this seems probable from the fact that in general paralysis and tabes the quantities increase with the progress of the decay. The process of decay will manifest itself in the earliest stages by an increased irritability and functional activity of the nervous structures, often manifesting itself in a *hyperæsthesia sexualis*, emotional exaltation, and, not infrequently, in striking intellectual activity, followed in each case by exhaustion and loss of function. In my second lecture I referred to the fact that the lipoids may be the

products of nuclear activity and the highly *phosphorised* nuclein may be really the source of vital action. We can, therefore, understand how detrimental a hyperæsthesia sexualis is to the vitality of the body.

The uselessness of antisyphilitic remedies is thus easily accounted for; indeed, they are generally positively injurious in true tabes and general paralysis because they lower the vital energy of a system which has over-immunised itself against the syphilitic virus. The only hope of doing any good is by an early diagnosis of the disease and suppression of all those exciting causes which use up the nervous energy and tend to overturn the normal metabolic equilibrium of the nervous structures. Other factors come in determining the location of the degeneration, and although microbial infections and microbial toxæmias are not directly responsible for these parasymphilitic affections, yet they may be an exciting agent in the onset of the disease, to the aggravation of the symptoms, to the acceleration of the progress of neural decay and the fatal termination.

I have often observed when influenza, dysentery, or pneumonia were prevalent in the asylums a number of general paralytics died after a succession of epileptiform or apoplectiform seizures, and I have found, *post mortem*, that they were suffering from one of these morbid infections. It is a common thing to find on the *post-mortem* table patches of broncho-pneumonia and recent active tuberculosis, the appearances of which would accord with clinical notes in the case-book reporting the occurrence of seizures; and, if the brain be examined microscopically, it is quite easy to prove that these fits correspond with acute degenerative changes, doubtless caused partially by congestive stasis and partially by a toxic condition of the blood exciting and accelerating the process of neural decay. Bacterial invasion, *secondary or terminal*, of the organs of the body of a *non-specific* nature, therefore, may accelerate the morbid process of decay or bring about a fatal termination.

In conclusion I wish to express my obligations to the President and Fellows of the College for their kind attention, as I am not unmindful of the distinguished lecturers who have preceded me; I feel that I have dealt imperfectly with a very difficult subject still in its infancy, but of the greatest importance to medical science and practice, and I can only hope that the words of the old philosopher, Lucretius, may come true, "that one thing after another will grow clear, and dark night will not rob you of the road, to keep you from surveying the utmost things of nature; in such wise things will light the torch for other things."

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A CASE OF GUMMATOUS MENINGITIS IN A CONGENITAL  
SYPHILITIC.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

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E. M. A. Female, aged 16 years. Admitted to Claybury Asylum 30/8/05, died 8/7/06. Previously a maid servant, and had done general work for her father for the last two or three years.

*History obtained from patient's father.*—Father, interviewed by me, gave the following history. His occupation had always been that of a coachman. No insanity on his or the mother's side. The mother of the deceased girl died when the girl was six months old. He married at the age of 20, his wife being a single woman before marriage, and a servant. I could obtain no history of venereal disease or excessive indulgence in alcohol. There were five children born alive, and three miscarriages. The first three pregnancies resulted in miscarriages, and then followed five children born alive, of whom the deceased girl was the last to be born. The rest of the children were all healthy and alive, with the exception of one little boy, who died at the age of nine years. I could obtain no information regarding the cause of the mother's death, except that she had dropsy.

The deceased girl was always delicate from birth. She had snuffles and convulsions, and was treated with grey powder. No history of rash. She was intelligent, quiet, and always reading, and nothing unusual was noticed until 18 months ago, when she became much quieter and forgetful, and would say funny things to her step-mother, and laugh if rebuked. About one year ago she suddenly left her father for no apparent reason, and went to her sister, with whom she stayed. Here she started singing and dancing, and became excitable; a doctor was sent for, she was removed to the infirmary, and thence to Claybury Asylum. The deceased girl never had any fits and was not of a worrying disposition. She fed and lived well. She was intelligent at school, and passed the sixth standard. The father married a second time, but at the present time there have been no children or miscarriages.

The patient, on admission to the Asylum, was considered to be suffering from congenital imbecility and mania. The case book notes state that she was excited, garrulous, and incoherent, singing snatches of comic songs and hymns. She appeared to be weak-minded, but her ability to

remember songs and their words was wonderful. It was observed that she was undersized, poorly nourished, and had Hutchinson teeth. (*Vide* Fig. III.) The knee-jerks were present, and there was slight internal strabismus of the right eye. The official notes from this time onwards are of no interest till the day before her death, when she is said to have had a seizure of the right side of her body and the left side of her face, followed by coma with stertorous breathing. There was an internal squint of the right eye. I obtained the following further information from the nurse: she was childish in her voice, speech, and actions, and amused herself with dolls and picture books, and made no attempt to read or write. (There must, therefore, have been considerable dementia, for I ascertained from the father that she had passed the sixth standard at school). She was faulty in her habits, but was afterwards sorry when corrected.

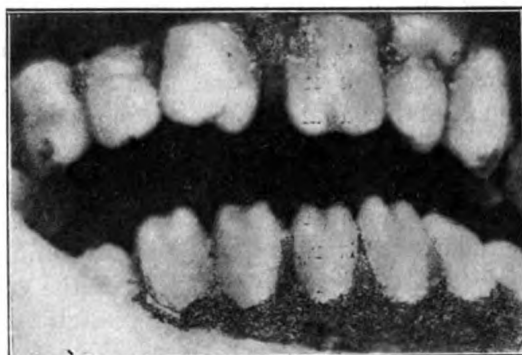


FIG. III.

Teeth of the patient. Photograph taken after death.

She was amiable, obedient, and affectionate, and a favourite with the nurses and patients. She had no delusions or hallucinations, and until the day before her death never had a fit. She would occasionally make mistakes as regards personal identification, and would call the nurse, mother. She never menstruated while in the Asylum. She took her food and enjoyed it. The songs she sang and her conversation did not lead the nurses to suppose that she had been immoral.

For three months before she died, she had stiffness and rigidity of the neck, holding her hand in such a manner that the doctor examined her several times for caries of the spine. She had then become helpless and drowsy, taking nourishment badly, and no longer singing her comic songs.

*Summary of autopsy.*—The brain weighed 1,125 grammes. It was soft and œdematous. There was excess of subdural fluid and the convolu-

tions were flattened. The convolutional pattern was good, and of average complexity; the Sylvian angle was also good. The whole of the base of the brain was covered with a greyish yellow deposit or membrane in places semi-fluid, but otherwise of fairly firm consistency and tough. On stripping this off, the brain substance beneath was left pitted, a similar condition was found on the orbital surface of the frontal lobes, and the mesial aspect whereby these were adherent. A greenish-yellow gelatinous semi-fluid material covered the anterior perforated spots and spread up the Sylvian fissures on both sides. On the under surface of the cerebellum there was a small maroon-coloured swelling. The vessels at the base of the brain and their extensions into the fissure were much thickened, and had a dirty greyish-yellow appearance, like dirty wash-leather. In places the lumen of the arteries of the circle of Willis was either partially or completely obliterated (*vide* Fig. 3, Plate IV.). The middle ear and nose were carefully examined to see if there was any cause for this meningitis, but without success. Cultures were made, and no pyogenic organisms were found. The ependyma of the fourth ventricle showed marked granulations.

The same deposit observed at the base of the brain was found extending down the spinal cord lying in the subarachnoid space. This greyish-yellow gelatinous exudation, after hardening in formalin, formed a firm tissue, which was especially thick in the region of the cervical enlargement, being there 3 or 4 mm. in thickness. The vessels and large arteries of the central nervous system appeared like solid cords or threads of varying thickness, they did not collapse on pressure. When cut through, the sections showed markedly thickened walls, and the lumen in some instances was obliterated.

The liver was denser than natural, otherwise there was no naked-eye change. The aorta showed slight atheroma. There was no evidence of tubercle, the lungs only exhibited bronchitis, congestion, and œdema.

Sections of the cortex cerebri, cerebellum, pons, medulla, optic nerve, arteries of the circle of Willis, and the spinal cord at various levels were made and stained by hæmatoxylin and eosin, and polychrome methylene blue and eosin.

#### HISTOLOGICAL CHANGES.

*Cortex cerebri.*—The meninges were infiltrated with lymphocytes and plasma cells, the pial vessels were markedly affected and the lumen diminished by this infiltration; in places where the meningitis was most marked, the infiltration was extending along the pial sheaths into the substance of the brain; but, as a rule, there was little or no change in the vessels in the cortical substance. The perivascular infiltration, then,



was clearly an extension from the meninges. There was little or no sub-pial felting or glia proliferation, and the columns of Meynert were not distorted in sections of the middle of the first frontal convolution. In the ascending frontal, however, there was much more evidence of affection of the vessels of the cortical grey matter; in fact, there was a very definite patchy encephalitis, and a very definite and abundant formative proliferation of the connective tissue cell elements of the small vessels and pial sheaths, so as to diminish or completely obliterate the lumen of the vessel. It seems that the process was an extension from the meninges, for it was much more marked on the superficial vessels.

In a section stained by hæmatoxylin and eosin of such a vessel examined with an oil immersion lens, the perivascular sheath—and even the lumen of the vessel—was filled with branching connective tissue-cells, the body and processes of which stained pink; lying in these pink-stained cells were purple, round, oval, and irregular nuclei in little clusters, the result of rapid division. The appearance was exactly the same as those observed in chronic trypanosome affections. The neuroglia cells appeared to be undergoing an active proliferation in the superficial layers of the cortex. In the cortical exudation and infiltration there were numerous plasma cells, and in places the neoplastic cell formation was undergoing a granulo-aqueous degeneration; plasmolysis and nucleolysis were very evident. Here could be seen the cells taking the eosin stain diffusely; they had a fainter and less brilliant staining reaction, and large numbers could be seen containing granules of chromatin of varying size. No micro-organisms were seen. The vascular changes indicating subacute meningo-encephalitis were very suggestive of acute general paresis.

*The cerebellum* showed the same periarteritis and endarteritis, and in the place where there was a maroon-coloured swelling, microscopic examination showed a hæmorrhage of some standing. All the vessels in the neighbourhood were profoundly affected in the manner described above and figured, Plate II., Figs. 4 and 5. The meningeal and perivascular and vascular neoplastic formation extended all the way down the spinal cord; it is shown in the accompanying photomicrographs, Figs. 1 and 2, Plate IV. No tubercle bacilli were discovered by appropriate methods of staining, no pyogenic organisms were obtained by culture, and no organisms were observed in the sections stained by polychrome-eosin to account for this meningo-encephalitis and meningo-myelitis. The infiltration around the optic chiasma was especially marked. It is difficult to understand why the child's sight was not more seriously affected, seeing that the perivascular infiltration had extended some distance into the chiasma. Very probably it was, but the child in the later days of its illness was in a too demented and stupid

state for it to be discovered. Curiously enough, although the child had a stiff neck and a squint, apparently no attempt was made to examine the fundus.

All the arteries of the circle of Willis showed profound periarteritis and obliterative endarteritis (*vide* Fig. 3, Plate IV.). The meningeal and perivascular neoplastic infiltration was universal; it corresponded entirely in its histological character with a gummatous meningo-encephalitis. Polymorpho-nuclears were conspicuous by their absence; the neoplastic formation consist of proliferated, branched, and spindle-shaped connective tissue-cells, and round or oval cells in which there was a distinct cytoplasm of varying thickness forming all grades between lymphocytes and plasma cells; there are also large macrophages. Large numbers of the cells were undergoing a granulo-aqueous degeneration, but the course of the disease was too intense and short to allow of absorption of the products of nucleolysis and plasmolysis and leave the connective tissue-cells to go on to the formation of fibrous tissue. Exactly the same sections of the cortex stained to display fibres showed some degeneration and destruction of the tangential system, but there was no marked evidence of sub-pial glia proliferation, nor was there any sub-pial felting; the perivascular infiltration clearly was an extension from the pia-arachnoid along the pial sheaths. Considering the universal vascular change and perivascular infiltration, it was astonishing how little destruction of cells and fibres had occurred. This can be correlated with the fact that there was comparatively little naked-eye wasting of the cortex. The cells in the superficial layers of the cortex are undoubtedly more affected than the deeper layers, and this is most marked in those patches of cortex where the chronic inflammatory process has extended most along the pial sheaths.

PLATE IV.

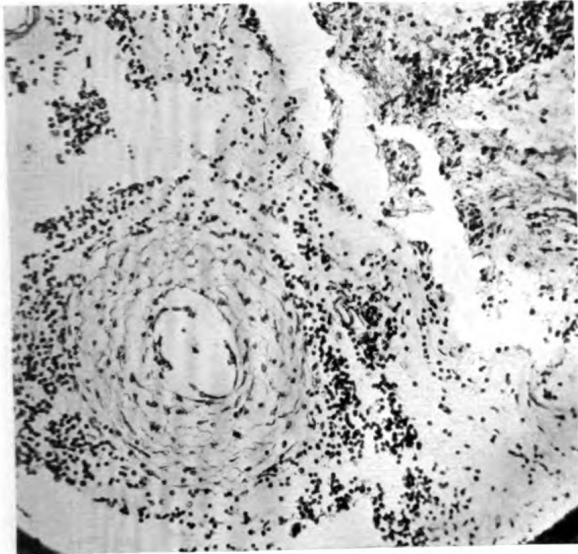


FIG. 1.

Section of lumbo-sacral spinal cord showing chronic gummatous leptomeningitis extending along the small vessels into the substance of the spinal cord. Mag. 200.

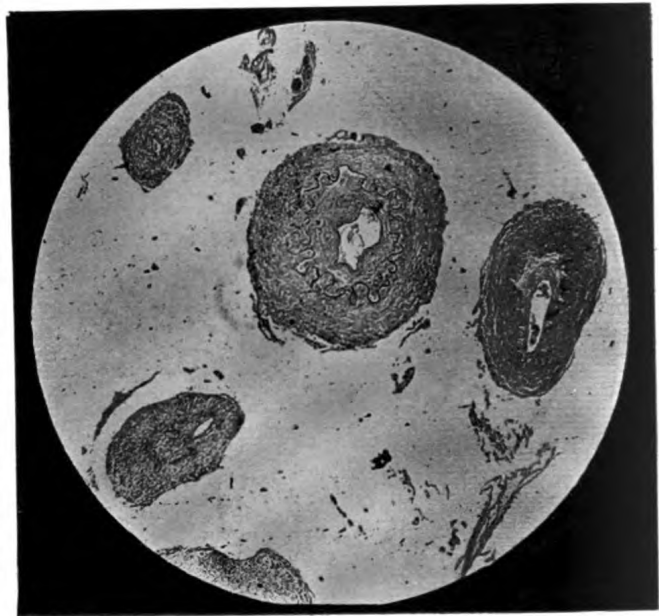


FIG. 3.

Section of various basal arteries showing obliterative arteritis. Mag. 15.

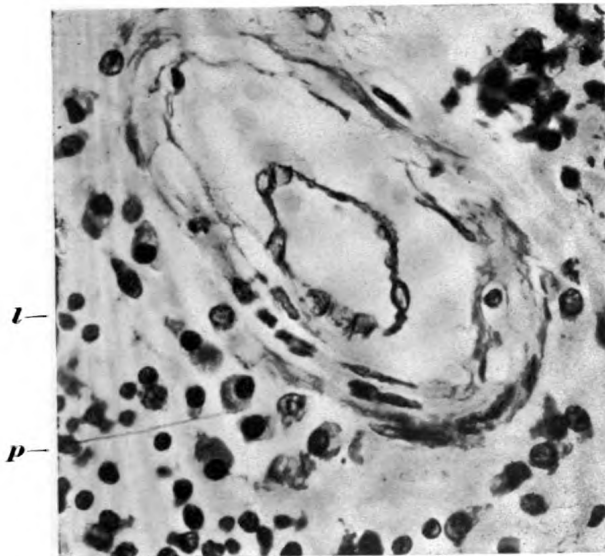


FIG. 2.

Section of the membranes showing the character of the formative cell hyperplasia, *l.* lymphocytes *p.* plasma cells. Mag. 700.

Face p. 62.

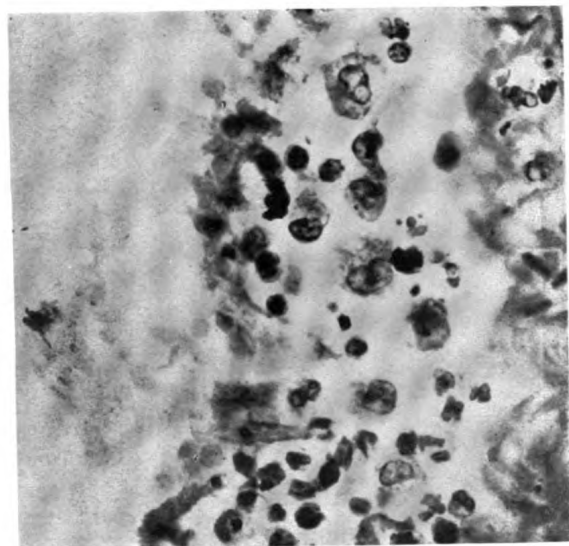


FIG. 4.

Section of the endarterium, showing lymphocytes and plasma cells undergoing granular degeneration. Mag. 700.



A CASE OF LOCALIZED SYPHILITIC PACHYMEINGITIS  
CEREBRI WITH SPEECH AFFECTION.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

A. G. Aged 44 years. Admitted to Hanwell 13/3/08 for epilepsy, loss of memory, and aphasia, from which she for a time improved. The history obtained showed that her husband had had syphilis eight years ago. She had been married over six years to him. She was his second wife, and has had no children or miscarriages by him. There were several papery scars on the body, and there was some slight glandular enlargement, but the signs of syphilis were not distinctive. Still, the symptoms pointed strongly to syphilis, and in my judgment it was desirable at once to push anti-syphilitic treatment with mercurial inunction after attending to a bad condition of pyorrhœa alveolaris and stomatitis.

I saw this patient on 17/5/08, my attention being called to the case by Dr. Daniel, under whose care she was. I found paresis of the right lower half of the face, with marked deviation of the tongue to the right. She was unable to close the right eye independently of the left, although she could wink and close the left eye independently perfectly well when asked to do so. There was some weakness of the right hand as compared with the left, and the deep reflexes were increased. She tried to talk, but her speech was hardly intelligible, although she understood all that was said to her, as was shown by her obedience to all commands and the endeavours she made to reply to questions; it appeared that her condition of speech defect might be due to dysarthria rather than aphasia, for her utterances were intended apparently to represent her silent thoughts. She is unable to read or write, and, therefore, could not be tested in this respect. I saw her in several fits. The fits come on quite suddenly; when asked whether she knows when a fit is coming on, she points to her tongue and lower half of the right side of the face. I asked her if she felt a numbness there, she responded in the affirmative. She does not lose consciousness, as she will obey commands while the fit is proceeding. The fit starts in a spasm of the muscles of the lower part of the right side of the face and jaw, this spreads up and down to the right orbicularis palpebrarum and corrugator supercilii, which are thrown into spasm, also the platysma of the neck. I thought there was some deviation of the eyes

to the right on one occasion, but she was able to look to the left when told to do so while the fit was proceeding. The spasm of the orbicularis palpebrarum spread to the opposite left eye and the eyeballs rolled upwards; it did not spread to the opposite lower face, nor did it spread to the arm. She has never complained of headache, but there was a tender spot on pressure just above the attachment of the left ear to the skull. There was no optic neuritis and no vomiting. The diagnosis I made was gummatous pachymeningitis over the region of the left ascending frontal and parietal convolutions at their lower extremity, involving especially the tongue area, also probably the pars basilaris of the third frontal.

#### SUBSEQUENT NOTES BY DR. DANIEL.

May 17th, 1908.—The notes state that the fits continue on an average about 50 a day. One fit lasted about 30 minutes (probably it was a series fused together), but it is interesting to observe *that she remained for 1½ hours unable to speak at all.*

May 20th, 1908.—She has had 50 fits in the night, and they are occurring every few minutes in the morning. Yesterday she complained of numbness and pains down the right arm. To-day *there is distinct deviation of the eyes to the right during the tonic stage of the convulsion*, and the fits are occasionally attended by loss of consciousness. She is now being treated by mercurial inunction twice a day.

May 26th.—The notes state that the fits now extend to the right arm, and various sedatives were given, including hyoscyin 1-50th grain, which, it is stated, has had a marked effect; she has had fewer fits and is markedly drowsy this morning; the pulse is feeble and rapid.

May 30th.—A difficulty in swallowing has been observed, and there seems to be an actual paresis. Fits continue practically uncontrollable.

June 1st.—The fits ceased, but patient died June 2nd at 4.35 p.m.

On June 3rd I made the *post-mortem* examination.

On removal of the calvarium, a pachymeningitis about the size of a florin was observed in the region of the tender spot noticed during life just three-quarters of an inch above the attachment of the left ear. On opening the dura mater the thickening was very definite. It was about five times as thick as the normal dura mater. This thickening was uniform, except at the circumference, where it gradually sloped off. It was red and inflamed both externally, in contact with the bone, and internally, in contact with the pia arachnoid. The bone in contact with the inflamed dura was roughened, and there was a slight degree of osteitis; the middle meningeal artery passed through the middle of the patch. Internally the pia arachnoid was red and inflamed, but there was no symphysis with the dura mater in this situation. One inch and a quarter

further back the dura mater was a little thickened (twice the normal) and adherent to the pia arachnoid, so that on stripping, erosion of the surface of the brain occurred over an area the size of a florin at the end of the fissure of Sylvius, involving the posterior end of the first temporal, the adjacent marginal, and, to a very slight extent, the angular gyrus.

Upon close examination the anterior patch of pachymeningitis showed several small caseous nodules about the size of a hempseed; it was found to be situated exactly over the lower end of the ascending frontal and the adjacent inferior frontal and ascending parietal convolutions. There can be no doubt that this gummatous pachymeningitis was the cause of the Jacksonian epilepsy; and it could have been removed by operation with the greatest of ease. At the autopsy no organic disease of other organs, nor of the brain itself, was found; and it was a great pity that the patient was not sent to a hospital as I recommended, for, in my judgment, it was a most suitable case for surgical treatment. She would have been transferred at once had there not been legal difficulties and formalities to overcome.

#### MICROSCOPICAL EXAMINATION.

I. Portions of the following structures were hardened in formalin and cut after being embedded in paraffin:—

(a) The syphilitic pachymeningitis, the cortex beneath comprising pars basilaris, ascending frontal and ascending parietal convolutions. A portion of the corresponding cortex of the right hemisphere was taken for comparison.

(b) Portion of the posterior part of the left first temporal and adjacent marginal convolution.

(c) The medulla oblongata at the level of the olivary bodies.

(d) The cervical enlargement of the spinal cord.

The sections  $10\mu$  in thickness were stained by Nissl, polychrome, Giemsa, Van Gieson, and Heidenhain eosin methods.

II. Portions of the tissues (a) and (b) were taken after the brain had been in formalin for 24 hours and prepared by the Cajal method.

#### DESCRIPTION OF HISTOLOGICAL CHANGES.

*The pachymeningitis.*—The fibrous bundles of the dura were swollen and separated by an infiltration of lymphocytes and plasma cells; these were unequally distributed, in places forming little nodular aggregations. Moreover, in some situations these collections of cells had undergone necrobiosis and transformation into a granular mass of detritus quite typical of a gumma. The sections showed the middle meningeal artery in transection, also some of its branches; the latter showed a

marked periarteritis, that is the adventia, was infiltrated with young cells; but the main trunk not only showed this condition, but also almost complete obliteration of the lumen by endarteritis. (*Vide* Fig. 4.)

*The cortex beneath the pachymeningitis.*—The pia arachnoid showed very little cell infiltration, and there was next to no extension along the pial sheaths of the vessels, and this accorded with the fact that there was no symphysis of the dura to the soft membranes. The superficial layers of the cortex exhibited a marked proliferative hyperplasia of the neuroglia cells (*vide* Fig. 5), especially evident in sections stained by all the methods mentioned when a comparison was made with the corre-



FIG. 4.

Photomicrograph of the middle meningeal in gummatous pachymeningitis.  
Magnification 85.

sponding cortex of the right side. (*Vide* Figs. 1 and 2, Plate V.) I do not think this glia proliferation could be accounted for by the wasting of the neural elements, but it was a direct expression of irritation caused by the superjacent inflammatory condition of the dura (possibly toxic chemical substances). There was some degree of atrophy of the tangential fibres, otherwise the fibre systems appeared as intact in this region of the left hemisphere as in the same region of the corresponding hemisphere. The columns of Meynert of the pyramidal layer were intact, the apical processes of the cells were straight, and



exhibited no cork-screw appearances; but it was possible that their ultimate termination, as well as the terminations of the Betz cells in the tangential layer were damaged or destroyed; otherwise the outline of the cells corresponded with the outlines of normal cells. By Nissl staining the cells showed large clear nuclei and a marked deficiency of chromophyllous substance. The tigroid substance was almost absent in the body of the cells and on the dendrons in sections of the left ascending frontal. A similar appearance was observed in the right ascending frontal, but it was not nearly so intense; there was more chromophyllous

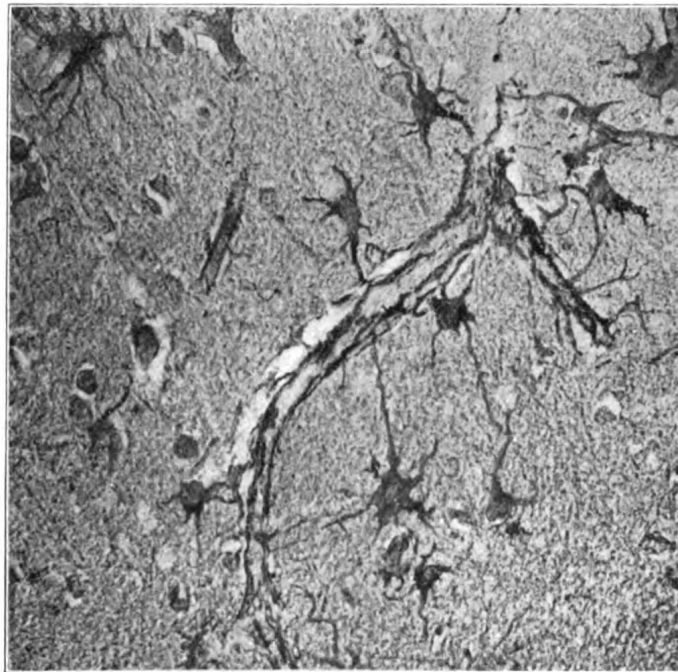


FIG. 5.

Photomicrograph of cortex of left facio-lingual area stained by Cajal fibril method; it shows remarkably well the neuroglia-cell hyperplasia and their extensions on to the walls of the small vessels. Magnification 330.

substance, and the cells stained less faintly. (*Vide* Figs. 1 and 2, Plate V.) By the silver method, fibrils could be seen running through the cells, and there was apparently not very much change.

The sections of the cortex at the end of the left Sylvian fissure exhibited very similar changes, but owing to the adhesion of the pia arachnoid to the dura, the cortex presented an eroded appearance; apparently the inflammatory process in this lesion started in the pia arachnoid instead of *within* the dura; it was more recent in origin and less extensive. There was a marked glia proliferation, and the same changes in the layers of cells noted in the other lesion.

*Medulla oblongata.*—Examination of the medulla oblongata showed a

marked diminution, and, in some cases, absence of chromatic substance in the cells of the facial, hypoglossal, and spinal accessory nuclei on both sides. It was thought that the right nuclei were more affected than the left, but it is difficult to be in any way positive about this. There could be no question that, compared with the appearance of the Nissl pattern of the cells in the anterior horns of the cervical enlargement, both the Betz cells of the motor cortex and the cells of the above-mentioned motor nuclei of the medulla oblongata showed a marked diminution of the chromatic substance; although some of the cells of the anterior horns of the spinal cord were not quite up to normal standard. From these facts it may be inferred that the cells where the primary lesion was acting as a cause of excitatory discharge, giving rise to Jacksonian epilepsy, exhibited the most notable signs of exhaustion, as measured by diminution or absence of chromatic substance. This could not be due to *post-mortem* change, because the cells of the anterior horns of the spinal cord showed a fairly normal Nissl pattern; nor, for the same reason, could the changes be due to the administration of drugs to control the fits prior to death, and it is permissible to assume that the most marked absence of Nissl granules observed in the cortex situated beneath the primary dural lesion may be explained as a result of exhaustion from discharge of energy in the local epileptiform fits produced by the local irritation. Subsequently the fits spread and became generalised, consequently the cells of the cortex of the right hemisphere showed some degree of exhaustion.

*Association of the symptoms presented during life, with the lesions observed post mortem.*—Undoubtedly the dysarthria and the Jacksonian epilepsy which I observed were in the main due to the pachymeningitis involving the lower end of the Rolandic fissure; but was the conjugate deviation (at that time hardly observable and certainly of later manifestation than the facio-lingual epilepsy) due to this lesion, or to the leptomeningitis involving the cortex behind the posterior end of the Sylvian fissure? The conjugate deviation to the right was only beginning to be manifested on May 17th, but later it became quite definite. In point of time of its initial manifestation it would coincide with the development of this lesion, although it might be explained by an extension of the zone of irritation caused by the anterior lesion, for clinical observation showed that the facio-lingual spasm was followed by tonic and clonic spasm of the right arm, at the time the conjugate deviation of the eyes to the right was noticed. It has been shown by Wilson that there is an association of pricking of ears and conjugate deviation of eyes. Moreover, cases have been recorded of conjugate deviation of eyes resulting from lesions in this temporal region.



PLATE V.



FIG. 1.

FIG. 2.

DESCRIPTION OF PLATE V.

FIG. 1.—Camera lucida drawing of small portion of left facio-lingual cortex beneath the pachymeningitis. The superficial molecular layer is shown and the fourth layer; the intervening pyramidal layers are not shown. It will be observed that in comparison with a similar portion of the cortex of the right hemisphere there is a marked hyperplasia of the neuroglia cells. These cells are undergoing active proliferation, the cytoplasm is markedly increased. There is a large Betz cell seen in which the Nissl granules are only very faintly seen, although the outline of the cell is not materially altered.

FIG. 2.—Camera lucida drawing of small portion of the right facio-lingual cortex. The glia cells are smaller, less numerous, and show but little hyperplasia as compared with those seen in Fig. II. A large Betz cell is shown; this exhibits a normal appearance, except perhaps the Nissl granules are not quite so large and distinct as in a normal brain.

Both Figs. 1 and 2 were drawings of preparations cut in paraffin, and stained with polychrome eosin. Magnification 500.

## TUBERCULOSIS IN THE LONDON COUNTY ASYLUMS.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

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## INTRODUCTION.

In consequence of a valuable communication upon the subject of tuberculosis in asylums by Dr. Crookshank, entitled "The Frequency, Causation, Prevention and Treatment of Pulmonary Phthisis in Asylums for the Insane," followed by a paper communicated by Dr. Eric France,

the Medico-Psychological Association appointed a Committee to investigate the matter. The conclusions arrived at were that:—

*(1) It is a fact beyond question that phthisis is prevalent in our public Asylums to an extent which calls for urgent measures, and that large numbers of patients contract phthisis after admission into the Asylums. (2) The special causes for this increased prevalence of phthisis are, in our opinion, overcrowding, with consequent insufficiency of hours in the open air; defects in ventilation and heating, uncleanly habits and faults in dietary.*

These conclusions were regarded in the main as being sound, but the statistical tables upon which they were based were thought in some respects to be unreliable, and consequently a revision was made by Dr. Chapman, whose deductions were as follows:—

*(1) Infection is one of the strongest causative elements in the prevalence of tuberculosis in Asylums. (2) A healthy, dry, and well-drained site is of extreme importance. (3) The causes of tuberculosis in Asylums inhere in the Asylums themselves and not in the character of the patients sent to them, although certain Asylums present exceptions.*

The value of these figures was materially impaired by virtue of the fact that the majority of them were not supported by *post-mortem* evidence. The statistics, therefore, depended largely upon the uncontrolled personal equation of diagnosis. The diagnosis of tuberculosis in the earliest stages in the sane is, as is well known, an extremely difficult matter, and it is generally admitted by all asylum medical officers that many and varied difficulties occur in arriving at a diagnosis of early phthisis in the insane. The patient resists examination or, if in a melancholic or stuporose state, the breathing is so shallow as to be difficult to hear, and often the patient cannot be induced either to take a deep breath or to speak. Again, many patients do not expectorate, and hence no sputum is available for examination for tubercle bacilli. For these reasons Dr. Eric France advocated the use of tuberculin as a means of diagnosis. Doubtless this would be a useful diagnostic measure, but, unfortunately, the test makes no distinction between obsolescent or quiescent tubercle and the active form of the disease, and isolation of all cases that reacted would, on the infective theory, lead to reinfection of quiescent cases. Moreover, we are not sure that the injection of tuberculin might not reignite a quiescent form of the disease. Calmette's ophthalmic reaction would not have this objection, but it might, as with tuberculin injection, lead to a wrong conclusion about the disease. For these reasons, I presume, neither of these methods have been generally adopted in asylums.

*Notification.*—The Pathological Sub-Committee of the London County Council, recognising the benefit that had resulted from the notification

of dysentery and the importance of the question of the prevention of tuberculosis, instituted, at my suggestion, a system of notification of all cases of tuberculosis in the London County Asylums. Monthly reports for the past five years have accordingly been made, affording the following information: Age on admission, sex, date of admission, ward, mental disease, date of discovery of tuberculosis, progress of the case, and ultimate result; if death, the *post-mortem* findings. These reports have been systematically collated by my assistant, Mr. Sydney Mann, and the data and deductions embodied in this communication are drawn from the statistical evidence thus afforded, together with the information from the records of the *post-mortem* examinations made at Claybury Asylum by myself or my assistants during the last ten years. Moreover, during one year, I personally conducted all the *post-mortem* examinations at Colney Hatch with a view to ascertaining whether the results corresponded with those at Claybury.

During the last eight years notification of all cases of dysentery and diarrhœa has been in operation in the London County Asylums, and it is satisfactory to know that the isolation of persons suffering from this disease has corresponded with a considerable diminution in all the asylums; it does not now attain to serious epidemics in wards as it did before this notification was instituted. Moreover, I do not see on the *post-mortem* table nearly so many cases of severe and acute dysentery at Claybury as heretofore. Nor is it a common occurrence as formerly for nurses, attendants, medical officers and employés in the asylum to suffer with dysentery as the result of an infection which could in many cases be definitely traced. These facts of themselves show the advantages of a system of notification, even if such notification only serves to call attention to the infectivity of the disease and the prevention of epidemics by isolation and other prophylactic measures. The Committee felt, therefore, that the same benefit might accrue from the notification of all cases of tuberculosis with a view to proper prophylactic measures.

*Comparison of ward incidence of dysentery and tubercle.*—Comparison of the ward incidence of these two diseases shows that in the case of dysentery there is ward incidence indicative of infection, although seldom now attaining a serious epidemic form. Before the notification and isolation of cases of dysentery I have known one ward of an asylum to have one-third of its patients suffering from the disease, the total number of cases amounting to many more than were contained in all the remaining wards in the asylum. Moreover, sometimes one asylum will notify at one period of time more cases than all the other asylums together. Now in the case of tubercle, the reports show no such special ward incidence, and I have systematically asked the superintendents and



medical officers whether they are able to furnish me with any reliable evidence pointing to an attendant or nurse acquiring tuberculosis in the asylums. Dr. Seward of Colney Hatch Asylum is of opinion that two attendants acquired tuberculosis owing to their being employed in a particular ward in that institution, and Dr. Jones of Claybury Asylum considers that some attendants may have acquired tuberculosis after entering the service, otherwise the replies have been in the negative (*vide* p. 90). This conforms pretty much with the experience of the Ventnor and Brompton Hospitals, as indeed with that of all sanatoria for consumption. It might, however, be argued that tuberculosis should *never* occur in a nurse or attendant, for all are examined as regards their general health upon entry of service.\* The obvious answer to this is that probably more than 20 per cent. of the presumably healthy adult public have obsolescent tuberculous lesions; the *post-mortem* findings at the asylums show the presence of obsolescent tubercle. Brouardel found that 50 per cent. of the bodies of persons who had met with violent deaths and had been taken to the Morgue in Paris presented tuberculous lesions. Dr. Harris, of the Manchester Royal Infirmary, found in 39 per cent. of all the necropsies evidences of tuberculous lesions. The few attendants who, after entering the service, develop tubercle may very well therefore have had quiescent tubercle which was undiscovered on examination. Under any circumstances the occurrence of the few cases of tuberculosis in a staff of over 2,000 cannot possibly be held to support any view that tuberculosis possesses a degree of communicability which is in any sense comparable with diseases such as smallpox, typhus fever and dysentery.

#### I.—INCIDENCE OF TUBERCULOSIS AMONGST LIVING PATIENTS.

The first table, which is subjoined, shows the number of patients who have been notified as suffering from pulmonary tuberculosis per 1,000 inhabitants in eight of the London County Asylums during the years 1904-1908 inclusive. The Epileptic Colony reports are for 1906-8 inclusive, and those of Long Grove Asylum, recently opened, only refer to 1908. These statistics appear to show a gradual yearly increase, but it is probable that the proportion for 1908 represents the more accurate figure, as many cases may have been overlooked during the first few years of notification.

Where notification has been adopted in towns and cities a similar apparent increase has been observed, although the measures adopted for

\* By resolution of the Asylums Committee (11th November, 1902), it was decided that all permanent officials be medically examined before their appointment be confirmed. Since that time more importance has been attached to the medical examination, and attendants and nurses have been subjected to a minor examination before they have been taken on probation, and to an examination in bed at the end of three months before their appointment has been confirmed.

prevention of infection have increased and improved, as indeed they have in the London County Asylums.

TABLE I.

Showing the total number of patients resident in the London County Asylums on March 31st of each year, with the proportion per 1,000 of those reported as phthisical.

	Number of Patients resident.		Number of cases of Phthisis reported.		Proportion per 1,000 residents.		
	M	F.	M.	F.	M.	F.	M. & F.
March 31st, 1904	7,065	9,705	129	144	18·2	14·7	16·2
.. 1905	7,196	9,816	149	155	20·7	15·7	17·8
.. 1906	7,238	9,850	165	170	22·7	17·2	19·6
.. 1907	7,311	9,916	141	192	19·3	19·3	19·3
.. 1908	8,276	10,714	176	217	21·2	20·2	20·7

We may therefore conclude that the probable number of cases of active pulmonary tuberculosis as diagnosed clinically among the insane in the London County Asylums is a little over 20 per 1,000.

The next table refers to the incidence at the various asylums during the same period. There is a marked variation in the cases reported per 1,000 inhabitants. It will be observed that Claybury is more than double any of the other asylums, and almost four times that of Cane Hill; it is not surprising that Cane Hill should report such a low incidence, for both the total death-rate and the percentage of active tubercle found *post mortem* are correspondingly low, whereas the total death-rate at Claybury is not much higher, but the percentage of cases with active tuberculous lesions at autopsy is very high. The variation which the table shows as regards the resident patients suffering from pulmonary tuberculosis may be explained to a small degree by the fact that some asylums more than others remove cases from the tuberculosis list as the symptoms become quiescent or subside, or on account of the diagnosis having been incorrect. But this does not nearly account for the surprising differences, and I consider that the personal equation of diagnosis is mainly responsible for the wide discrepancy. Taking the returns from all the London County Asylums, we find that 25 per cent. of the cases showing active phthisis at autopsy are not diagnosed during life, and the difficulties in the way of correct diagnosis are demonstrated by the following figures from Claybury, where the necropsies are made by independent skilled pathologists and microscopical examination is made in doubtful cases.

During the five years, 162 cases notified during life as phthisical have come to autopsy; the diagnosis was confirmed in 111 cases (68·5 per cent.), but in another 86 cases the presence of active pulmonary tuberculous lesions was noted only at autopsy. As mentioned elsewhere, a large number of the latter cases were general paralytics. Only those who have had practical acquaintance with the diagnosis of pulmonary complaints in the insane can appreciate the many difficulties which arise in large asylums in respect to the detection of tuberculous cases. Probably if the *post-mortem* examinations had been made under the same conditions at the other London County Asylums similar figures might have been obtained. This certainly shows the necessity of a more certain mode of detection of tuberculous cases than at present exists, if isolation is to be effective in preventing the dissemination of the tuberculous organisms, either in the form of dust or droplets.

TABLE II.

Showing the proportion per 1,000 of the patients resident in the various London County Asylums reported as suffering from active phthisis.

	Ban- stead.	Bex- ley.	Cane Hill.	Clay- bury.	Colney Hatch.	Han- well.	Hor- ton.	The Manor.	The Colony.	Long Grove.
March 31st, 1904	14·2	13·3	12·7	33·6	12·7	14·9	13·1	13·3	*	*
.. 1905	14·3	19·4	8·9	38·1	17·9	15·9	13·3	9·3	—	*
.. 1906	16·0	23·1	8·8	42·9	21·4	16·0	11·8	7·7	6·1	*
.. 1907	12·2	24·9	9·8	40·8	19·1	16·2	13·4	11·4	9·2	*
.. 1908	17·5	20·3	13·1	46·3	22·2	15·1	15·1	11·0	8·9	17·2
Average ...	14·8	20·2	10·6	40·3	18·6	15·6	13·3	10·5	6·0	17·2

It is probable that the returns at Bexley represent about the average incidence per 1,000 residents, namely, 20.

*Time of diagnosis.*—The majority of the cases, as Table III. shows, are not diagnosed until some time after admission, and it would appear that the disease in the majority of the cases had been acquired in the asylum, but the *post-mortem* findings at Claybury and Colney Hatch, where I made the necropsies for one year, do not, in a general way, bear out this conclusion. As already pointed out, there are many difficulties in the way of diagnosis especially in the early stages of the active disease, particularly in the discovery of obsolescent tubercle.

TABLE III.

Showing the time of diagnosis of tubercle of the total number of reported tuberculous patients resident in the London County Asylums on the 31st March of each year.

	1904.	1905.	1906.	1907.	1908.	Average for 5 years.
Disease diagnosed on admission	71	78	101	88	120	91.6
Disease diagnosed within one year of admission ... ..	44	44	53	46	42	45.8
Disease diagnosed after one year of admission ... ..	158	182	181	199	231	190.2
Total ... ..	273	304	335	333	393	—

Seeing that one medical officer has charge of 500 patients this disease can easily be overlooked in the early stages, and attention may not be called to a case until the symptoms become plainly urgent, and either wasting or obvious illness is visible to the attendant or nurse in charge. The patients themselves, as a rule, do not complain, but when a patient becomes stuporose or melancholic, refuses food and loses weight—signs of mental and bodily depression—then tuberculosis may be suspected and looked for. In a great percentage of necropsies signs pointing to obsolescent tubercle in the form of scars at the apices with caseous or calcareous deposits, caseous or calcareous bronchial glands, or sometimes mesenteric glands, and old pleurisy with adhesions are so frequently found in association with active tuberculosis that it becomes a difficult matter to decide whether the active disease is due to reinfection from without, or reawakening of the original quiescent disease. Whichever it be, the signs of obsolescent tubercle point to a soil that is suitable to the growth of the tubercle bacilli; and with the lowered *vita propria* of the tissues the resistance has been so diminished that the patients are unable to withstand the disease. Special attention has been given to this point by the pathologists at Claybury for the past six years. An attempt has been made to approximate the length of time the patient has suffered with the disease, a task difficult enough. It would be impossible, even after long experience, to give precise data, and no more can be said than that the great majority of the cases appeared to have had either obsolescent tubercle before admission or active tuberculosis on admission. In the early stages of active phthisis, as is well known, the disease may be discovered by systematically taking the temperature in

the early morning and late afternoon for at least a week. I am not aware that this is done at any of the Asylums on admission of new cases. A large proportion of patients suffering with active phthisis do not expectorate, therefore the opportunity of examining their sputa does not occur. I have been surprised at the few specimens which have been sent for examination, although an offer has been made to examine at the Pathological Laboratory the sputum of any doubtful case.

## ASSOCIATION WITH MENTAL CONDITION.

TABLE IV.

Showing mental condition of all reported tuberculous patients in the London County Asylums, resident on the 31st March of each year.

—	1904.	1905.	1906.	1907.	1908.	Average for 4 years.
Acute Insanity ... ..	86	49	56	42	60	52
Subacute Insanity ... ..	13	5	7	5	11	7
Chronic Insanity ... ..	137	102	113	123	129	117
Melancholia ... ..	*	101	106	104	126	109
General Paralysis ... ..	5	8	8	5	6	7
Epilepsy c. Insanity ... ..	15	19	17	23	24	21
„ c. Imbecility ... ..	*	7	7	6	11	8
Imbecility and Idiocy ... ..	17	13	21	25	26	21

Owing to the different nomenclature and classification employed at the various Asylums, it was found very difficult to correlate the reports of the mental condition associated with tuberculosis. It was therefore decided to adopt the following classification: (1) Tubercle diagnosed within one year of onset of mental symptoms; (2) tubercle diagnosed within 12 to 18 months of onset of mental symptoms; (3) tubercle diagnosed after 18 months of onset of mental symptoms. These are termed respectively acute, sub-acute, and chronic insanity. Subsequent to the first year of notification, the large number of cases returned as melancholia were collected under one heading. The cases of melancholia are all cases of mental depression, and would include many cases of manic-depressive insanity and dementia præcox, as well as melancholia. In Table IV. it will be observed that melancholia figures largely as the mental condition associated with tuberculosis; this is not surprising, as it

may be supposed that the mental depression is correlated with a nutritional failure of the whole body, including the brain; the establishment of a vicious circle occurs whereby mental depression and bodily depression interact, the *vita propria* suffers, and micro-organismal infection readily takes place. There are many reasons that melancholy, and especially melancholic stupor, should be associated with active tubercle. The patients have no appetite or desire for food, they not only do not enjoy their food, but often have a positive dislike for it or view it with distrust, and, refusing to take nourishment, they have to be fed with a nasal tube; even when care is taken, some few drops of the fluid food may find their way into the bronchial tubes and lead to broncho-pneumonia. The general inertia of the patient is associated with shallow respiration, enfeebled circulation, and malassimilation; and there is a depressive fall of all the vital energies, so that the resistance to tubercular infection is much diminished by the mental condition. The relatively few cases of mania with excitement as compared with melancholia are striking. Imbeciles, epileptics, and paralytics are, for similar reasons, susceptible to tubercular infection or reawakening of obsolescent disease. The large number of cases of chronic insanity (disease diagnosed some time after the onset of mental symptoms) include those which, for the most part, show old tubercle at the *post mortem*, and it would appear that a reactivity or reinfection has taken place with the gradual lowering of the patients' resistance, caused by the mental and physical deterioration. The reported incidence among paralytics is slight, but reference to the *post-mortem* statistics shows that a comparatively large number of paralytics exhibit active tuberculous lesions at autopsy. Seeing that from 20 to 30 per cent. of the cases that come to autopsy are patients who have suffered with this form of insanity, this may account for the divergence of statistics of active tubercle found *post mortem* at Claybury, as compared with other Asylums having an equally high total death rate, *pro rata*, for the population. The tuberculous process becomes active and progressive in the later stages of this disease when there is marked mental and physical deterioration, but in the majority of the cases there are signs of obsolescent disease, with reactivity.

In the Asylums under the control of the Metropolitan Asylums Board where chronic incurable lunatics, idiots, and imbeciles are housed, tuberculous disease is more prevalent than in the London County Asylums. (*Vide* p. 103). Relatively only a few epileptic imbeciles, imbeciles, and idiots are resident in the London County Asylums.

*Age at time of diagnosis.*

TABLE V.

Showing the age at the time of diagnosis of tuberculosis of the reported living phthisical patients in the London County Asylums on the 31st March of each year.

Age.	1904.	1905.	1906.	1907.	1908.	Average for five years.
10-19 years	11	7	7	6	9	8
20-29 "	47	50	60	58	70	57
30-39 "	84	96	106	96	106	98
40-49 "	63	74	81	94	101	83
50-59 "	47	52	49	43	61	50
60-69 "	16	20	25	31	38	26
70-79 "	4	4	6	4	6	5
80 "	—	1	1	1	—	1

It will be observed that, in a large number of the cases, tuberculosis is diagnosed early in life (50 per cent. under 40 years of age); the majority of these are cases of dementia præcox, imbecility, and idiocy, and cases of melancholia,—manic-depressive insanity. Reference to the *post-mortem* statistics will show that these cases run a comparatively rapid course and die early.

These figures do not include the cases in which the disease was diagnosed for the first time at autopsy, but they give a fairly accurate proportion, for, whereas a number of general paralytics dying early in life come to autopsy with undiagnosed tubercle, there is a balancing number of cases of chronic insanity, dying later in life, in which an active lesion is discovered for the first time at autopsy, the lesion generally being a reactivity of an obsolescent area.

Although the above statistics may indicate approximately the incidence of tuberculosis among the living patients and the relation to mental disease, without reference to the records of autopsies, they are liable to give rise to many erroneous conclusions, for a number of cases are diagnosed for the first time *post mortem*, other reported cases show no evidence of active disease at autopsy, and in many cases the mental condition may so mask the physical symptoms of the disease that the date of onset is not correctly stated.

I am unable to find any reliable figures regarding the incidence of phthisis among the sane living inhabitants of London for comparison with the figures given above.

*Deaths with active pulmonary tuberculous lesions in the London County*

*Asylums, 1st April, 1903, to 31st March, 1908.*

The statistics for the past five years relating to the autopsies at all the London County Asylums have been collected, and a summary of *all the cases of active phthisis* has been made. The results are given in the following Tables:—

TABLE VI.

Showing for each year (1st April to 31st March) the total number of deaths, total number of autopsies, and the total number of cases presenting active phthisis in percentage of total *post-mortems*.

	Number of Deaths.		Number of <i>Post-mortems</i> .		Number of Deaths with active Phthisis.		Per cent. of Deaths with active Phthisis of total <i>Post-mortems</i> .		
	M.	F.	M.	F.	M.	F.	M.	F.	M. and F.
1904	720	665	640	609	92	100	14.3	16.2	15.3
1905	763	627	660	544	101	94	15.3	17.3	16.2
1906	722	719	612	619	82	75	13.4	12.1	12.7
1907	798	796	724	691	103	100	14.2	14.4	14.3
1908	741	738	668	682	88	122	13.2	17.8	15.5
Total	3,744	3,545	3,304	3,145	466	491	14.1	15.6	...
Total M. & F.	7,289		6,449		957		14.8		

During the five years April 1st, 1903, to March 31st, 1908, 7,289 deaths have occurred in the London County Asylums; autopsies have been made in 6,449 instances, and active pulmonary tuberculous lesions found in 957 cases (466 M, 491 F), *i.e.*, 14.8 per cent. of the total *post-mortems*. Of these tuberculous cases, 241 (127 M, 114 F), or 25 per cent., were not diagnosed during life, and it is interesting to note that 79 (62 M, 17 F) of these cases were general paralytics.

The females appear to be more affected than the males, but the Claybury *post-mortem* statistics (page 95) show that among the non-paralytic population the males are more affected than the females.\*

It will be observed that the incidence of tuberculosis at the various Asylums shows a great variation. The causes of this variation may be sought in the following conditions:—

1. The structure, mode of heating, ventilation, size of wards, and cubic space allowed for each patient at each of the ten institutions;

\* The monthly reports which during the past five years I have received from Banstead Asylum, owing to some misunderstanding on the part of those who made the returns, were incorrect, and I take this opportunity of stating that the statistics regarding tuberculosis in that Asylum which have been published in the annual reports for the past five years are invalid. The whole of these reports were returned, and the Superintendent was kind enough to see that they were amended.



County Asylum

HANWICK

Number of Deaths.	Number of Autopsies
217	198
216	182
240	209
214	199
210	182
1,097	970

4



100

Long Grove.	The Manor.	Epileptic Colony.	Total.
56	8	7	638
16	4	4	250
33	11	14	505
13	3	1	164
55	2	6	447
40	10	11	591
134	47	35	1,262
57	20	12	563
13	4	2	165
71	38	19	1,136
36	14	6	628
103	17	10	1,013
71	23	20	758
15	6	—	162
18	5	—	163
33	18	4	418
27	21	9	373
61	53	11	808
42	14	1	433
36	6	8	354
33	29	9	431
103	50	28	1,232
8	4	1	161
41	18	5	560
87	42	34	852
94	63	15	1,154
81	77	20	1,158
26	10	12	374
46	9	14	548
45	11	11	405
84	13	—	540
1,578	650	329	18,246

2. The situation of the asylum as regards soil, altitude, and climatic conditions, and time the patients spend in the open air;

3. The scale of dietary, the provisions for ensuring a milk free from tubercular germs;

4. The type (age, sex, and class) of patients, and numbers of transfers admitted from out-county Asylums;

5. The personal equation of the superintendent and medical officers at the various asylums in respect to the diagnosis of tuberculosis during life, and the confirmation, or otherwise, *post mortem*, which is apparently by far the most important factor.

If there be a constant low death rate associated with a constant low tuberculous death rate at a particular asylum, it may be assumed either that the type of patient received in that Asylum is different, or that some one or more of the conditions under Groups 1, 2, and 3 are more favourable to the patients resident in that Asylum. For example, Cane Hill Asylum has a comparatively low death rate and a low percentage of cases which showed active phthisis at the autopsy. I have endeavoured to ascertain whether the varying incidence of tuberculosis at the different asylums could be attributed to any difference in the class of patient admitted. The accompanying figures show the number of patients resident in each London County Asylum on January 1st, 1908, chargeable to the poor law authorities of the several London districts.

If we compare the two asylums that present the highest and lowest mortality with tuberculosis (*i.e.*, Claybury and Cane Hill), we find that Claybury is chiefly inhabited by the insane brought from the east and north-east districts of London, whereas Cane Hill receives mostly the insane of the districts of South London, notably Southwark and Lambeth, which localities, according to Booth, are quite as poor as the eastern districts. South London may be more salubrious than the East End, but both districts have their poverty-stricken areas, with attendant overcrowding, &c., and I do not think there is evidence to show that the difference in the type of insane inhabitant influences to any marked degree the incidence of tubercle at the respective asylums. Moreover, I find that all of the London County Asylums receive a good number of patients taken from the more non-salubrious areas of London, and, speaking generally and from observation, I should say that the various asylum populations, on the whole, are practically of the same class. I would make the exception of Colney Hatch, to which Asylum the Jewish insane and the few young epileptic imbeciles housed in the London County Asylums are sent. The Manor Asylum has nearly all female patients resident, and presents a fairly high incidence of tuberculosis, but this asylum has only 600-700 inhabitants, and is hardly comparable

with asylums thrice its size. The varying incidence cannot be attributed to a different scale of dietary, for, practically, that is the same in all the asylums; moreover, there is no reason to believe that the milk supplied to the patients has been less likely to have been infective at the one than the other asylum.

The difference in the incidence of active tuberculosis must be referred, therefore, to either the structure of the respective institutions, mode of heating, ventilation, size of wards, and cubic space allowed for each patient, *or* to the site of the asylum as regards soil, altitude, and climatic conditions. I regret that I am unable to give any reliable data concerning the death rates from phthisis for the various asylum districts.

If we compare the two oldest asylums, Colney Hatch and Hanwell, with Bexley and Cane Hill, we might assert that the difference was due to the structure, &c.; but Claybury is a comparatively new asylum, and as regards structure compares most favourably with any of the other London County Asylums, we can only conclude, therefore, that a high death rate, and the especially high percentage of cases of active tuberculosis found *post mortem*, may be partially associated with the site, soil, altitude, and climatic conditions. Claybury Asylum is situated on a hill, the soil is heavy clay, many of the airing courts are exposed to the east wind, which blows across the damp Essex marshes, and I think this unfavourable climatic condition may perhaps partially account for the higher incidence of active tuberculosis found *post mortem* than in the other asylums, *e.g.*, Colney Hatch, Hanwell, and Horton Asylums, which are also situated on clay. Banstead Asylum has apparently a low incidence of tuberculosis, and this we might attribute to its healthy site; unfortunately, it has a high death rate, for which there may be the explanation that diseases other than tubercle are more prevalent there than at Cane Hill and Bexley, *e.g.*, pneumonia, dysentery, &c.

As regards the low tubercular incidence, some cases of general paralysis dying with active tuberculosis may be regarded as bronchopneumonia, especially as I have found that cavitation is less frequent with the tuberculous paralytic. (*Vide* Table XIII.)

Were it possible to eliminate the personal equation in the compilation of statistics, the facts here adduced would appear to point to the general conclusion that soil, site, and climatic conditions are of considerable importance in reference to the incidence of tuberculosis in the insane of the London County Asylums. Thus, Cane Hill and Banstead (with the reservations mentioned) are situated on chalk hills, and the percentage of cases which, at *post mortem*, showed active tuberculosis were, respectively, 12·33 and 10·85. Bexley, at a fairly high altitude, on gravel and sand, has a percentage of 11·83. whereas Hanwell and Colney Hatch,

*Age at time of death.*

TABLE VIII.

Showing age at time of death of the patients dying with active tuberculous pulmonary lesions, in the London County Asylums during the five years (April 1st, 1903 to March 31st, 1908).

—	1-4-03—31-3-04.			1-4-04—31-3-05.			1-4-05—31-3-06.			1-4-06—31-3-07.			1-4-07—31-3-08.			Total for five Years.		
	M.	F.	M.&F.	M.	F.	M.&F.	M.	F.	M.&F.	M.	F.	M.&F.	M.	F.	M.&F.	M.	F.	M.&F.
Age at death —																		
10-19 years ...	3	—	3	3	3	6	2	—	2	2	—	2	2	2	4	12	5	17
20-29 „ ...	11	14	25	20	16	36	12	16	28	19	13	32	15	19	34	77	78	155
30-39 „ ...	20	30	50	29	23	52	28	14	42	25	26	51	22	29	51	124	122	246
40-49 „ ...	21	24	45	20	18	38	16	25	41	22	30	52	23	29	52	102	126	228
50-59 „ ...	17	16	33	20	19	39	7	14	21	18	15	33	10	25	35	72	89	161
60-69 „ ...	11	12	23	8	13	21	13	3	16	14	13	27	10	12	22	56	53	109
70-79 „ ...	9	3	12	—	2	2	3	3	6	3	2	5	4	6	10	19	16	35
80 — „ ...	—	1	1	—	—	—	1	—	1	—	1	1	2	—	2	3	2	5
TOTAL																466*	491	957

both on clay and low lying, have percentages of 16·29 and 18·92 respectively. Claybury has a very high percentage, viz., 21·67 per cent. At first glance these figures look very convincing against Claybury as compared with Banstead, Bexley, Colney Hatch, and Hanwell, but the total death rate at Claybury in proportion to the ratio of the population is not higher than Bexley, Hanwell, or Colney Hatch. (*Vide* Table VII.) But, in all these, the total death rate is considerably higher than at Cane Hill. The probable explanation of the high incidence of active tuberculosis at Claybury, as compared with the other asylums, *except Cane Hill, with its low death rate and low percentage of active tubercle at death*, lies in the fact that all the *post mortems* at Claybury are made by a skilled pathologist, who gives special attention to the discovery of the tubercle bacilli by microscopic examination in all doubtful cases of broncho-pneumonia, and this applies particularly to the broncho-pneumonia occurring in general paralytics, in which cases there is frequently either an infection or else reinfection from obsolescent tubercle.

Table VIII. shows that over two-thirds (67·5 per cent.) of the deaths with active phthisis in the insane die under the age of 50 years, also that the maximum number of deaths with phthisis occurs between 30 and 39 years of age. It is well recognised that one of the great characteristics of pulmonary tuberculosis is its tendency to attack and kill those at the working, marriageable, and reproductive periods of life; thus, in the case of the insane, it tends to eliminate the unfit at an early age. Dr. Tatham points out that in England and Wales as a whole, and in the urban group of counties, the age of highest mortality from tuberculosis is at ages from 45 to 55 for males, and at 35 to 45 for females. In the rural group it is from 25 to 35 for both sexes; but in the year 1905 the greatest incidence in England and Wales and in the urban counties was 35 for females and 45 for males.

*Comparison of the Phthisis Death Rates at the several Age Periods for the Sane and Insane.*

The subjoined Table, comparing the phthisis death rates for 1907 at the several age periods per thousand living in London and per 1,000 of the total population (18,872) resident in the London County Asylums has been rendered possible by the kindness of Sir Shirley Murphy, who has supplied me with the phthisis death rates at the several age periods per 1,000 *sane* persons living in London for 1907. I have also compiled a summary of the cases from all the London County Asylums during 1907 in which phthisis was the cause of death; these figures have been obtained by analysis of the *post-mortem* records, and also of the addition of the



few cases that did not come to autopsy, but in which phthisis was the assigned cause of death.

TABLE IX.

Showing a comparison of the phthisis death rates for 1907 at the several age periods per 1,000 sane living in London, and per 1,000 of the total insane population (18,872) resident in the London County Asylums.

—	Sane per 1,000 living.	Insane per 1,000 living.	Insane Incidence.
Age period—			
15-19 years ...	0·71	12·1	17 times as great as sane
20-24 " ...	0·96	13·4	14 " "
25-34 " ...	1·56	19·8	13 " "
35-44 " ...	2·49	15·1	6 " "
45-54 " ...	2·92	6·1	2 " "
55-64 " ...	2·57	7·8	3 " "
65 years and over...	1·62	6·8	4 " "
Totals ... ..	1·33	11·1	8 times as great as sane

The following interesting facts may be deduced from the above Table:—(1) The much greater incidence of deaths from phthisis in adolescence and up to 35 years of age in the insane than the sane; (2) the deaths after 45 years of age are only double those of the sane. It is, however, necessary to qualify these figures by certain facts: (1) The majority of the people admitted to the asylums are either bodily enfeebled, and with very low powers of resistance, or are suffering with actual bodily as well as mental disease; therefore, the probable average duration of life is infinitely less than the outside population of the same class; (2) the sane population would include all grades of society and not the pauper class alone; (3) twenty-five per cent. of the people who die are general paralytics, and these only live a few years after admission, and, as we have seen, a large proportion, especially of the females, die with active tuberculosis; (4) the statistics of the sane are not controlled by *post-mortem* examination.

Consequently, the figures given above must be considered as only approximate, and they probably over-estimate the incidence of tuberculosis among the insane as compared with the same pauper class of the sane. Still, however, these figures show that tuberculosis and insanity, especially some forms of insanity, are intimately associated. The Table also seems to show that insanity diminishes considerably the average duration of life of the tuberculous individual.

*Racial incidence of tuberculosis.*—Dr. Bulstrode, in his very interesting lecture at the Royal Institution, referred to evidence which went to show that the Irish suffer unduly from tuberculosis, even when they have left their native land; and he contrasted the Irish with the Hebrew race, which, from the statistics available, appear to possess a marked immunity to the disease. The Commissioners in Lunacy for Ireland have called attention to this heavy prevalence of tuberculosis, and to the increase of insanity in that country. The former is regarded by them as being due to the pauperism, insufficient nourishment, and bad hygienic conditions under which the people live, especially those who are “feeble-minded,” and, therefore, less fit for employment and less capable of earning sufficient money to obtain proper food. It is probable that the high incidence of insanity may be due in a measure to the more mentally fit having migrated to America; still, if there is a high incidence of tuberculosis among the Irish-American population, it may be contended that there is a racial tendency to the development of phthisis.

Colney Hatch Asylum receives all the Jewish insane, for the most part alien. I therefore determined to see how these Jewish lunatics compared with the Christians as regards incidence of tuberculosis. I was not able to control the result by the data obtained on the *post-mortem* table, for Jews are all “conscientious objectors.” Still, the results are of interest. I am much obliged to Dr. Seward for furnishing me with the following data: “The total number of Jewish patients who died during the five years (April 1st, 1903, to March 31st, 1908) was 75 males, 69 females; total, 144. Of these, 21 males, 16 females, total 37, had active tuberculous lesions. As very few *post-mortem* examinations are made in the case of Jewish patients, it is necessary to make some allowance for a few cases in which the disease may not have been recognised during life.”

This makes 25·7 per cent., which rather under-estimates the number, yet it exceeds considerably the incidence among the Christians at Colney Hatch Asylum, which, for the same period, and controlled by *post-mortem* examinations, was 18·9 per cent. It may be asked how we account for this? I think it is because the Jewish patients are largely composed of aliens who have not been long in this country; they come from Russia, for the most part, where they and their progenitors have lived in great pauperism and degradation, and, therefore, unlike the prosperous Jews, whose progenitors settled in this country several generations back, have already the seeds and soil of consumption in their bodies when they arrive in this country.

Prof. Karl Pearson, from his investigations upon inheritance, comes to the following general conclusions as a result of his study of the statistics of pulmonary tuberculosis:—

“(a) What I have spoken of as the diathesis of pulmonary tuberculosis is certainly inherited, and the intensity of inheritance is sensibly the same as that of any normal physical character yet investigated in man.

“Infection probably plays a necessary part, but in the artizan classes of the urban populations of this country, it is doubtful if their members can escape the risks of infection, except by the absence of the diathesis, *i.e.*, the inheritance of what amounts to the counter-disposition. The probably earlier age of onset, at least in certain cases of family history, as compared with those cases without family history, cannot at present be definitely asserted to be due to parental infection. In the statistics we are dealing with, the bulk of the parents must have passed the danger zone before the onset to the offspring (average age: 29 for males and 25 for females), and further, many such offspring will already have left in the artizan classes the immediate home environment. The earlier age of onset in the children is probably associated with the same tendency to earlier inheritance noted in cases of cancer and defective vision and possibly in gout, rheumatic fever and diabetes, where the question of infection hardly arises.

“I feel fairly confident that for the artizan class the inheritance factor is far more important than the infection factor, because in a very large proportion of cases it does not lie in the power of the individual to maintain in the stress of urban life a wholly safe environment.

“(b) There is no reduced fertility in the case of tuberculous stocks, in fact their fertility is as great as that of any other class in the community, and markedly greater in artizan tuberculous stocks than in any class of brain workers.

“(c) In general, whether we deal with all tuberculous stocks, or only with those having no parental history, the elder offspring, especially the first and second, appear subject to tuberculosis at a very much higher rate than the younger members.

“The one certain rule of racial fitness is the preservation of the dominant reproductivity of the mentally and physically fitter stocks. In less civilized communities than our own this is roughly provided for by the struggle for survival within the race and between races, and by the fight against organic environment and against physical environment. As far as statistical facts as to inheritance, fertility and survival in civilized communities are at present known and available, the dominant reproductivity of the mentally and physically fitter stocks appears likely to be more and more weakened by (1) the lessened intensity of the intraracial struggle, and (2) the differential limitation of the family.

“Can we consciously do what in the past was unconsciously achieved; can we preserve this dominant reproductivity of the mentally and physically fitter stocks? If this is to be done at all, we must patiently continue to collect data as to disease, inheritance, and fertility in man. There must be a healthy co-operation between medically and statistically trained minds, and when the evidence is, as I believe it will be in the near future, overwhelming, then there must be a united effort of both to influence public opinion in favour

first of a few simple rules of conduct for those social by nature, and then, if necessary, a further united effort in favour of legislation to restrain those anti-social by inheritance or nurture."

The reports furnished in the system of notification at the asylums did not yield sufficiently reliable data to prepare any useful statistics, and, though I possess at present no precise data, yet I am of opinion, from experience, that inheritance of a *soil* suitable for the development of tuberculosis is associated so frequently with certain forms of insanity, notably those with mental depression and which begin when the reproductive functions commence, that although I do not consider Clouston is warranted in speaking of a tuberculous insanity, *per se*; nevertheless, a metabolic failure at the reproductive period is at the basis of both the insanity and the tubercular infection. At this period of life the specific vital energies of all the somatic tissues are subjected to a test of their fitness to fulfil the reproductive functions, and provide directly or indirectly the necessary nutrition for the offspring. All the metabolic activities are increased, especially of the highly complex phosphorus-containing substances; the nucleo-proteids and lipoids.

Dr. Tatham says: "In both sexes it is with the approach to maturity that the real liability to death by phthisis begins, and this is true of recent as well as earlier years." In persons who do not inherit an insane temperament, an invalid brain, the existence of tuberculosis does not lead to failure of the nutrition of the brain, unless there be actual tubercular infection of that organ. It is not surprising that the brain inherently sound should not suffer materially in its functions from malnutrition, seeing that it does not undergo wasting in starvation or the most severe forms of anæmia; unless there be marked toxæmia or pyrexia, or, as generally happens, the two combined, no mental disturbance occurs. This may be explained by the fact *that the preservation of the individual* necessitates the preservation of the most noble master tissues, even at the expense and destruction of the less noble tissues which are its servants. Again, the *preservation of the species* is instinctively so powerful that tuberculous individuals, though not possessing sufficient *vital energy* and nutritional reserve to maintain metabolic equilibrium and resist the invasion of the tissues by the tuberculous organism, nevertheless, do not suffer as regards fertility until the disease has advanced to an incurable stage. It is probable that the inheritance of a *soil* suitable for the development of the tuberculous organism is dependent upon some metabolic failure which is transmitted. There is some evidence to show that in the case of dementia præcox, there is transmitted also a metabolic failure of the brain itself. (*Vide* paper by Dr. Koch and Mr. Sydney Mann).

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Sir Hugh Beevor advances the proposition that it is the power of the growing lung to resist infection which determines different incidence of the disease on sex at early ages. At a time when most persons are highly prone to nearly all the specific infectious diseases, and when the lungs are, he thinks, exposed to tuberculous infection as much as at any other age, the death rate from pulmonary tuberculosis is relatively insignificant. It is, in his view, the full-grown lung of the girl of fifteen years of age, which, having lost its resistance to the tubercle bacillus, leads to the death rate of the 15-year-old girl from phthisis being equal to the boy at 17. But the 15-year-old girl is sexually mature, and the sexual instinct is stirring to the full degree the vital energies of all the tissues; this sexual instinct develops later in the boy, and I conceive that it is this instinctive change in the metabolic activities of the somatic tissues to provide nutrition for the reproduction and preservation of the species at an earlier age in the female than the male, that lowers the powers of resistance to the tubercular organism of the inherently feeble.

*Incidence of phthisis amongst asylum officials.*—All employes in the London County Asylums are now subjected to a medical examination before admission to the service (*vide footnote*, p. 73), consequently it is to be presumed that few if any cases of active phthisis enter the service. The medical examination is now enforced, but it was not in past years.

TABLE X.

Showing the approximate length of Service of the Attendants and Nurses in the various London County Asylums in October, 1908.

Length of Service.	Male Attendants.		Total.	Female Attendants.	Total M. & F.
	Resident.	Non-resident.		Resident.	
Under 1 year	139	6	145	400	545
1 year to under 3 years	195	38	233	396	629
3 years " " 5 " "	56	53	109	198	307
5 " " " 10 " "	74	213	287	220	507
10 " " " 15 " "	8	103	111	82	193
15 " " " 20 " "	5	95	100	49	149
20 " " " 25 " "	3	29	32	17	49
25 " " " 31 " "	—	16	16	4	20
Total	480	553	1,033	1,366	2,399

It will be observed that 52 per cent. of the male attendants, and about 30 per cent. of the nurses have been in the service five years or more.

There are about 2,400 attendants and nurses employed in the London County Asylums, and at present the following five cases are notified as phthisical:—

		Date of entering Service.		Date of diagnosis of Phthisis.		
CLAYBURY—						
Att. A. C.	...	30-5-98	...	May, '03	...	Now at work in wards. Disease quiescent.
Att. J. C.	...	23-2-03	...	2-5-05	...	" " "
Nurse A. P.	...	24-7-94	...	?	...	" " "
COLNEY HATCH—						
Att. W. W.	...	1-5-93	...	about 1896	...	Now at work in wards. Disease quiescent.
Att. D.	...	23-9-02	...	10-6-07.		

Thus, of these five cases present on the list as presumably tuberculous, four have resumed their duties in the wards, the disease being therefore quiescent, or the diagnosis was doubtful.

With regard to the incidence among the staff in past years, and also the question whether the disease was acquired while in the asylum service, I have received the following replies from the various medical superintendents:—

**Dr. Johnston Jones, Banstead Asylum,**

States that three attendants and seven nurses have suffered with tuberculosis during the past fifteen years. The family history in each of these cases showed a strong tendency to the disease. In his opinion no nurse or attendant has acquired the disease in the service.

**Dr. Stansfield, Bexley Asylum,**

Has reported the following cases during the past five years:—

		Entered Service.		Tubercle Diagnosed.		
Att. H. G.	...	12-9-01	...	Nov. '05	...	Given 3 months leave and then left service.
Att. A. E. B.	...	20-6-04	...	12-4-06	...	Left service August, 1906.
Nurse G. S.	...	16-8-00	...	16-3-03	...	Left service 31-12-03.
Nurse G.	...	21-5-01	...	5-3-03	...	Left service March, 1903.
Nurse F. M. S.	...	23-6-05	...	Nov. '05	...	Left service January, 1906.

**Dr. Moody, Cane Hill Asylum, states:—**

"As far as I am aware no attendant or nurse at present here is suffering from tuberculosis. Since the opening of the Asylum (1883) I can remember two nurses and two attendants who had the disease, but as we did not examine officials before entering the service I cannot say if they acquired it here or no."

**Dr. Robert Jones, Claybury Asylum:—**

"During the last five years, 1904-8, five male attendants died of pulmonary tuberculosis; one has left the service from the same cause, whilst three remain. These three have each been resident in a sanatorium for at least three months, and the symptoms of tuberculosis are at present in abeyance.

No nurse has died in the Asylum from tuberculosis, but several have died after leaving the service, which they did through ill-health, viz., tuberculosis in the early stage.

It is suspected that at least three other nurses are at present suffering from tuberculosis.

I consider the soil of the Asylum site somewhat favours tuberculosis, being heavy clay and subject to undue mists and frequent fogs from the river and low-lying flats.

The medical examination of candidates for Asylum service excludes cases of definite tuberculosis, but in the early stages it is no easy matter to be dogmatic as to the presence or otherwise of tuberculosis. The fact that a medical re-examination is made at the end of the six months' probationary period certainly tends further to exclude this disease from amongst the staff, so that those who contract it do so most probably from the nature of their work and surroundings.

That this percentage is small among the staff may be gathered from the fact that there are about 157 female and 133 male attendants, but to fill these posts, during the five years, 270 nurses and 145 male attendants have been engaged—a total of 415 persons, so that there has been considerable fluctuation among the resident staff. Of these, 81 attendants and 42 nurses have been in the service over the five years referred to, being in the proportion of 61 per cent. and 27 per cent. respectively of the male and female attendants."

#### Dr. Seward, Colney Hatch Asylum,

Reports the following cases among the staff, and is of the opinion that two attendants who were employed in an insanitary ward probably acquired the disease in consequence.

#### INCIDENCE OF TUBERCULOSIS AMONG THE MALE ATTENDANTS AND NURSES.

All Attendants and Nurses are carefully examined before joining the service, and those mentioned below were passed as healthy.

Name.	Commencement of Service.	Termination of Service.
Att. J. M. ....	2nd March, 1877 ....	1st February, 1888 (resigned).
Att. J. C. ....	5th April, 1878 ....	30th September, 1888 (resigned).
Nurse B. A. G. ....	1st January, 1889 ....	19th May, 1890 (resigned).
Att. A. J. ....	12th May, 1890 ....	28th June, 1890 (unfit for duty).
Att. W. A. W. ....	1st April, 1887 ....	8th June, 1891 (died).
Att. J. J. ....	1st March, 1880 ....	2nd July, 1895 (died).
Att. A. B. ....	31st January, 1883 ....	25th September, 1896 (died).
Att. E. F. ....	9th December, 1882....	17th July, 1899 (died).
Att. G. B. ....	17th December, 1894 ....	5th March, 1902 (died).
Att. E. A. ....	29th November, 1904 ....	10th October, 1908 (died).
Att. W. W. ....	1st May, 1893 ....	Still in the service.
Att. H. D. ....	23rd September, 1902 ..	Still in the service.

W. J. SEWARD,

*Medical Superintendent.*

30th October, 1908.

## Dr. Bailey, Hanwell Asylum,

Reports the following cases:—

		Date of entry to service.		Date of diagnosis of tubercle.		
Nurse A. H.	...	26-7-88	...	Dec. 1902	...	Left service 16-11-03.
„ E. C.	...	22-3-06	...	Dec. 1906	...	Left service 11-2-07.
„ N. V.	...	19-9-99	...	Jan. 1907	...	Left service 27-4-07.

The last two have since died.

Att. J. W. G.	...	16-12-96	...	Sept. 1904	...	Died 23-1-05.
„ W. F.	...	5-3-01	...	Sept. 1904	...	Withdrawn from list 30-1-06.
„ G. H. P.	...	15-4-01	...	March 1906	...	Died 12-8-06.

## Dr. Lord, Horton Asylum, states:—

“Regarding the prevalence of phthisis amongst the staff, my short experience at this asylum does not permit me to give you exact figures, but speaking generally I think it is a comparatively rare thing for nurses and attendants to acquire the disease. I understand that here there have been three or four attendants who have suffered from phthisis, but in every case a strong family history of tuberculosis was present, and there was a degree of doubt as to whether or not the seeds of the disease were not sown prior to their admission here. Only one attendant has been reported as phthisical since I have been here, but the signs in the lung were indefinite, and after his death I was told that he had suffered from cancer. One of the nurses who has a strong tubercular history, had an irregular temperature for some months during the early part of the year without any pulmonary signs.”

## Dr. Donaldson, Horton Manor:—

“I append herewith a list of nurses who left the asylum service owing to having developed phthisis:—

		Date of joining service.		Date of leaving service.
Nurse K. M.	...	28-8-02	...	31-12-02
Nurse A. P.	...	7-3-02	...	5-8-02
Nurse A. R. J.	...	16-7-06	...	11-3-07

The above-named were all medically examined on admission, and no signs were detected, although in some of the cases the disease may have been latent. A nurse, E. P., who was here from 8th March, 1903, till 13th July, 1905, resigned owing to ill-health; there was a suspicion of phthisis in her case. I believe also that an attendant, J. G., who joined here on the 28th August, 1899, and left on the 7th November, 1900, developed phthisis whilst here. I am unable to inform you definitely with regard to his case, as he left the asylum, owing to ill-health, before I came here.”

## Dr. Spark. The Epileptic Colony:—

“No attendant has to my knowledge acquired phthisis at the Colony. There is at present an attendant with an abscess, possibly of tubercular origin, but I do not consider that the tubercle has been acquired in the Colony.”



Dr. Bond, Long Grove Asylum, opened June 18th, 1907:—

“No member of the staff has so far contracted tuberculosis since entering the service.”

It will be observed that, of the cases noted, the majority developed the signs of tubercle after a short period of service, three years or under, some few, indeed, died of the disease within 6 to 18 months of admission.

Table XI. shows the approximate length of service of the inspectors, matrons, and head attendants in the London County Asylums. It will be observed that nearly 90 per cent. have been five years or more in the service, and the majority 15 years or more. Now, those who have had twenty years' service, and they are 51 out of 137, have been located—at any rate, for a great part of their service—in the old, and, presumably, less sanitary asylums; yet, they have not been infected, or, if they have been, they have undergone spontaneous cure, for I have not heard of a case of tuberculosis occurring in a head attendant.

TABLE XI.

Showing the approximate length of Service of the Matrons, Inspectors, and Head Attendants in the London County Asylums.

Length of Service.	Male.	Female.	Total.
Under 5 years ... ..	3	12	15
5-10 years ... ..	10	22	32
10-15 „ ... ..	6	14	20
15-20 „ ... ..	6	13	19
20-25 „ ... ..	11	15	26
25-30 „ ... ..	8	10	18
30-35 „ ... ..	5	—	5
Over 35 years ... ..	2	—	2
Total ... ..	51	86	137

It is impossible to compare these statistics with the outside population, but if asylums were as infective as was supposed by the report of the Medico-Psychological Association, one should have expected a much higher incidence of tuberculosis among those employed for 14 hours daily in actual attention to the lunatic. Moreover, length of service appears to point to freedom from tuberculosis among nurses and attendants, for the disease was recognised in those reported, in the majority of instances, during the first few years of service.

II.—SUMMARY OF STATISTICS RELATING TO TUBERCULOSIS FOUND *post mortem* AT CLAYBURY ASYLUM FROM SEPTEMBER 1ST, 1898, TO AUGUST 31ST 1908.

The records of tuberculosis occurring in the bodies of nearly all the patients dying at Claybury Asylum during the above ten years may be summarised as follows:—

All the necropsies have been made by the pathologist or his assistants during that period. In 90 per cent. of the total deaths an examination has been made, and the observations systematically recorded. In every case every organ, including the bowel, has been carefully examined, and particular attention has been paid to discover the existence of obsolescent tubercle. In cases of doubt, examination for tubercle bacilli has been made.

During that time 2,203 (1,075 M., 1,128 F.) deaths occurred, and necropsies were made in 1,982 cases (961 M., 1,021 F.). Active tuberculous pulmonary lesions were found in 215 female and 201 male cases; total, 416, *i.e.*, 20·9 per cent. of the total *post mortems* (20·9 per cent. M. and 21·0 per cent. F.).

Pulmonary tuberculosis was judged to be the primary cause of death in 323 cases (149 M. and 174 F.); 16·3 per cent. of the total *post mortems* (15·5 per cent. M., 17·0 per cent. F.).

This figure does not compare with the percentage mortality on the total deaths from all causes for the ten years (January 1st, 1898, to December 31st, 1907) given in the Commissioners' Report, but the difference can be explained. Firstly, there must always be some difficulty in deciding which is the primary or immediate cause of death when two or more factors are concurrent. Secondly, there are a number of cases in which the symptoms of tuberculosis are masked by the mental condition, and in which tuberculosis, although sufficiently advanced as to cause death, is not diagnosed except at autopsy. It will be seen, on reference to the statistics of the association of tuberculosis with mental condition (p. 101) that a good proportion of general paralytics die with active tuberculosis; the disease in these cases is hardly ever diagnosed during life (p. 80), and, although in many cases it is purely a secondary associated condition, in many others it is extensive and active enough to have been correctly assumed to be the primary cause of death. The above figures are taken from actual *post-mortem* records, and in each case—if the tuberculous lesions alone were judged sufficient to cause death, tuberculosis was assigned as being the primary cause. The personal equation of the various medical officers at the London County Asylums,

other than Claybury, who each make autopsies on their own cases, must vary considerably in respect to this important point of deciding in cases of general paralysis whether it should be recorded that the patient died of general paralysis or concurrent tuberculosis.

Tuberculous ulceration of the intestines was found in 73 males (36·3 per cent.) and 115 females (53·4 per cent.) of the cases dying with active tuberculous lesions; in the latter case the higher percentage is possibly due to the fact that females are more apt to swallow their sputum than males.

TABLE XII.

Showing the incidence of phthisis amongst general paralytics, with comparison according to the age at death, with the incidence of phthisis among non-paralytics during the ten years 1-9-98 to 31-8-08.

	Fifty years of age and under at death.			Over 50 years of age at death.			Total.		
	M.	F.	M. & F.	M.	F.	M. & F.	M.	F.	M. & F.
Total number of autopsies	468	429	897	493	592	1085	961	1021	1982
Total number with active phthisis	129	149	278	72	66	138	201	215	416
Percentage with active phthisis	27·5	34·7	30·9	14·6	11·1	12·7	20·9	21·0	20·9
Total number of general paralytics	274	110	384	82	23	105	356	133	489
Total number of general paralytics with active phthisis	52	30	82	8	5	13	60	35	95
Percentage of general paralytics with active phthisis	18·9	27·4	21·3	9·7	21·7	12·3	16·8	26·3	19·4
Total number of non-paralytics	194	319	513	411	569	980	605	888	1493
Total number of non-paralytics with active phthisis	77	119	196	64	61	125	141	180	321
Percentage of non-paralytics with active phthisis	39·6	37·3	38·2	15·5	10·7	12·7	23·3	20·2	21·5

The onset of general paralysis occurs usually in the third or fourth decade of life, and death occurs in the majority of cases before the patient has arrived at the age of 50. If we wish to make a fair comparison between the incidence of active tuberculosis at death between general paralysis and other forms of insanity, we should compare corresponding periods of life. The above table shows that in 1,982 *post-mortem* examinations, active tubercle was found in 20·9 per cent., the female incidence being practically the same as the male, viz., 21·0 and 20·9 per cent.; but if we take the non-paralytics, we find a higher incidence among the males, viz., 23·3 per cent. males and 20·2 per cent. females, and this

agrees with the relationship of pulmonary tuberculosis in the outside population, where the males preponderate. Among the general paralytics we find a reversal of this order of things, viz., 16·8 per cent. males to 26·3 per cent. females, and it is this difference which makes the total female incidence of active phthisis found *post mortem* very slightly in excess of the male incidence. Now we may ask the question, why should female general paralytics show a higher incidence of active pulmonary tuberculosis *post mortem*? Is it because there is more liability to infection in the Asylum? I think not, for, as a rule, female general paralytics live longer after admission than males; I consider the answer is afforded by the relative social position of male and female general paralytics. It is well known and acknowledged that the higher we rise in the social scale, the less frequently do we meet with this disease in females. *Vice versâ*, the lower we descend in the social scale, the more prevalent does it become, so that in the pauper classes the ratio of general paralytics is about three males to one female, perhaps less for a considerable proportion of the male paralytics admitted as pauper lunatics have only become paupers since the onset of the disease which deprived them of their money, their business, their occupation, and, in not a few cases, their profession. I have been struck by the fact that, whereas the friends who visit male paralytics frequently belong to the middle as well as the lower classes, it is seldom that the friends of the female paralytic belong to the middle classes. Many of them, although spoken of as married women, belong, or did belong, to the unfortunate class who earn their living by prostitution, and are not visited by friends. The frequency with which one finds non-tuberculous adhesive inflammation of the oviducts (50 per cent. of the total female general paralytics that die) lends indirect support to this contention. Another interesting fact, which Dr. Watson and I observed in the comparative examination of a large number of brains, was the relatively inferior convolitional pattern and weight of the brains of female general paralytics as compared with male paralytics. Quite 30 per cent. exhibited a convolitional pattern indicative of defective mental endowment, as if their possessors belonged to the congenital feeble minded. It is generally acknowledged that syphilis is the cause of this disease, and the history of sterility, miscarriages and still-births which is so frequently found in female general paralytics, together with other reasons, supports the contention that the reason that the female paralytics show a much higher incidence of active pulmonary tuberculosis than the males does not rest upon the fact that they are more likely to acquire the *seeds* of tuberculosis in the Asylum, but that the social conditions under which a good number of them lived prior to admission, of exposure to cold and wet,

of insufficient nourishment, *poverty*, overcrowding, and alcoholism, combined with an inborn mental and physical deficiency in a considerable percentage, produced a more suitable soil for the development of tuberculosis.

In the 35th Annual Report of the Local Government Board, 1905 and 1906, Dr. Bulstrode remarks: "Although there are doubtless many factors influencing the prevalence of tuberculosis, there is one that stands out prominently above all others; this factor is poverty, and although it is matter for dispute which elements of poverty are mainly operative, there is much evidence in support of the view that poverty as a whole, with all that it comprises and implies, may be regarded as one of the most, if not the most potent predisposing causes of the malady."

Sir Shirley Murphy, in his reports, has called attention to the correlation of pauperism and overcrowding with tuberculosis in various districts of the County of London.

The increasing death rate from tuberculosis in Ireland in association with a high total pauperism and increase of insanity points to pauperism being productive of both conditions, as the Inspector in a supplement to the 54th Report of the Inspectors in Lunacy says: "It would seem not improbable that the innutritious dietary and other deprivations of the majority of the population of Ireland must, when acting over many generations, have led to impaired nutrition of the nervous system, and in this way developed in the race neuropathic and psychopathic tendencies which are the precursors of insanity."

TABLE XIII.

Showing percentage of cases of active phthisis found *post mortem* during the ten years, 1-9-98 to 31-8-08 with cavitation. Comparison of paralytic and non-paralytic cases.

	Non-paralytics.			General Paralytics.			Total.		
	M.	F.	M. & F.	M.	F.	M. & F.	M.	F.	M. & F.
Number of cases with active phthisis	141	180	321	60	35	95	201	215	416
Number of cases with cavitation	88	133	221	32	19	51	120	152	272
Per cent. of cases with cavitation	62.4	73.8	68.8	53.3	54.3	53.6	59.7	70.7	65.3

In Table XIV. it will be observed that practically 25 per cent. of the cases of deaths with active phthisis occurred within a year of admission to the asylum; even if allowance be made for the fact that the combination of the mental affection with the bodily disease hastens the

fatal termination, it is more than probable that tubercular disease either preceded or coincided with the onset of the mental symptoms.

TABLE XIV.

Showing the length of residence in Asylum of the cases dying with active phthisis during the ten years, 1-9-98 to 31-8-08.

Length of residence.	Males.	Females.	Totals.
Under 3 months ... ..	16	13	29
3 months to under 6 months ...	21	13	34
6 " " 9 " ...	11	10	21
9 " " 12 " ...	11	5	16
12 " " 18 " ...	19	15	34
18 " " 2 years. ...	13	17	30
2 years " 3 " ...	25	29	54
3 " " 4 " ...	18	25	43
4 " " 5 " ...	10	20	30
5 " " 6 " ...	11	16	27
6 " " 7 " ...	12	19	31
7 " " 8 " ...	12	9	21
8 " " 9 " ...	4	7	11
9 " " 10 " ...	4	7	11
10 years and over... ..	14	10	24
Totals ... ..	201	215	416

Of 416 cases of patients dying with active pulmonary tuberculosis 164 died within two years of admission; it is probable *a priori* that the great majority of these patients suffered with tuberculous lesions on admission, albeit the disease was not diagnosed on admission in a large percentage of this number. It will be observed that practically 70 per cent. of the cases died within five years of admission to the asylum. In the next five years we have a marked drop in the deaths, which decrease does not accord with Dr. Chapman's deduction based upon the statistics of the Medico-Psychological Association, viz.: "The cases of tuberculosis in asylums *inhere in the asylums themselves and not in the character of the patients sent to them.*" If this were correct there should be a steady increase of the deaths with active tuberculosis for each year of residence. Colney Hatch is the second oldest (opened 1851) of the London County Asylums; and when I made the *post-mortem* examinations there for one year I had the opportunity of examining the bodies of patients who had been in residence from 30 to 50 years, and I did not find in some of these a trace of tubercle. I cannot therefore agree with Dr. Chapman's deduction. My contention, moreover, is supported by the following *post-mortem* records:—

TABLE XV.

Showing incidence of obsolescent tuberculosis without active disease in total *post-mortems* at Claybury Asylum during the six years, 1-4-02 to 31-3-08.

Signs pointing to obsolescent disease.		Active disease.		Nil.		Total.	
M.	F.	M.	F.	M.	F.	M.	F.
179	144	122	122	267	264	568	530
TOTALS... 323		244		531		1098	

Thus 323 cases, or 29·4 per cent. (31·5 per cent. males and 27·1 per cent. females), showed signs of obsolescent pulmonary tuberculosis without any active disease; active or obsolescent lesions, or both, were found in 51·6 per cent. of the total *post mortems*.

TABLE XVI.

Showing probable time of infection of the cases dying with active pulmonary tuberculosis at Claybury Asylum during the six years, 1-4-02 to 31-3-08.

Probably infected before admission.		Probably infected after admission.		Doubtful.		Total.	
M.	F.	M.	F.	M.	F.	M.	F.
77	90	13	12	32	20	122	122
TOTALS... 167		25		52		244	

Thus in only 10·2 per cent. of the cases with active phthisis at autopsy was it inferred by *post-mortem* examination that the disease had been acquired in the asylum.

The above tables are based upon the records of autopsies made at Claybury Asylum; they must, however, be considered as only affording approximate truths, for there are many and varied difficulties of determining accurately the data upon which they are based. If a patient, on the one hand, has been a short time in the asylum, and we find evidence of obsolescent tubercle there is no difficulty in asserting that the patient had suffered with the disease before admission, even if there be associated active disease; it does not, however, prove whether the reinfection was from within or from without; all that it shows is that there was a suitable soil for the seed to grow upon. On the other hand, if the patient

dies some few or more years after admission it may be very difficult to decide whether the obsolescent tubercle should be regarded as evidence of the patient having suffered with tubercle before admission. Still, the fact that 323 cases, or 29·4 per cent. (31·5 per cent. males and 27·1 per cent. females), showed signs of obsolescent pulmonary tuberculosis without any active disease indicates that a large percentage of the residents in the asylum have a *soil* suitable for the development of tuberculosis, yet have not developed active disease by infection from without. This does not support Dr. Chapman's contention that the majority of the cases of pulmonary tuberculosis in asylums are due to infection owing to causes inherent in the asylums themselves, otherwise we ought to find relatively only few cases of spontaneous cure among the residents in asylums, whereas it is nearly as high as in the outside population. The time elapsing between the onset of definite symptoms and the fatal termination varies considerably according to the form of the disease and the resistance of the individual. Is the institutional life more unfavourable than the home life of the patient? I think not in the case of pauper patients, as the food is wholesome, plentiful and nutritious in the asylums; the patients spend a considerable time in the open air, and, although large numbers are collected in day rooms and wards, the air is infinitely better, both as regards purity and temperature, than in the majority of the overcrowded, badly ventilated and badly drained homes of the London poor. These conditions, together with warm clothing and medical attention, should to some extent counterbalance the effects of the mental disease in making a comparison of the average duration of life after active pulmonary phthisis has been diagnosed. It is impossible to make comparisons with the pauper sane classes, about which there are no corresponding *post-mortem* data, nor with the cases attending a hospital for consumption, *e.g.*, the Brompton Hospital. We have no definite facts to determine what is the average duration of the disease in a similar class of the sane population, but it is probable that the Director of the Henry Phipps' Institution at Philadelphia is right when he asserts: "The correct duration of the disease, however, should be measured from the implantation, and this implies a long period of dormancy in most cases. The probabilities are that tuberculosis is always primarily a lymphatic disease, and that the lymphatic period is always dormant, except when the disease manifests itself by an enlarged superficial gland." The report further expresses the view that in the past medical men have usually measured the duration of the disease by the period of mixed infections. The active destruction and ulceration with cavitation is largely due to associated septic organisms. Lunatics, especially those subject to fits, loss of consciousness, dementia, or who have to be fed



by a nasal tube, are especially liable to broncho-pneumonia owing to fluid nourishment entering the bronchial passages. Such a condition in a patient with obsolescent tubercle would light up the disease again, or if there were no previous tubercular infection, form a very favourable soil for infection from without. Thus we often find calcareous bronchial glands or an old cicatrix at the apex in a lung in which there is active broncho-pneumonic phthisis due to a mixed infection.

Occasionally I have found calcareous mesenteric glands, and, in an autopsy I made at Colney Hatch Asylum on an imbecile youth, I found an acute tubercular pleurisy which I ascertained was due to infection through the diaphragm by a broken down mesenteric gland which had formed an abscess. The other mesenteric glands were caseous and calcareous throughout. There could be no doubt that, although the boy was not suspected of having phthisis on admission, he did not develop this tubercular mesenteric affection during his residence of less than two years in the asylum. Probably the infection occurred in early childhood and spontaneous cure had occurred.

I have made necropsies on patients who have died from active tuberculosis, and the notes in the case book have decidedly pointed to the acquirement of the disease since admission, yet careful *post-mortem* examination has shown the existence of old lesions, that must certainly have been present long before the patient was admitted. Occasionally, but rarely, I have made autopsies in which I could find no evidence of old tubercular lesion in the way of glands or cicatrices, yet I have discovered that the physical signs on admission pointed to one apex being affected, or I have occasionally ascertained from friends that the patient had attended a hospital for consumption. In such instances there has been a breaking down ulceration and cavitation destroying the original quiescent focus of disease.

*Association with mental condition.*—As there are no certain data forthcoming upon which to make statistics in regard to the mental condition of the tuberculous insane, it was necessary to divide the forms of mental disease into the following groups:—

TABLE XVII.

Showing the mental condition of the cases dying with active phthisis during the ten years, 1-9-98 to 31-8-08.

Form of Insanity.	Males	Females.	Total.
Epileptic insanity ... ..	5	9	14
Epileptic imbecility ... ..	4	—	4
Imbecility and idiocy ... ..	9	5	14
General paralysis ... ..	60	35	95
Melancholia ... ..	58	91	149
Other forms of insanity ... ..	65	75	140
Totals ... ..	201	215	416



It will be observed that idiots and imbeciles are relatively few in number, but they are for the most part not admitted to the London County Asylums, but are sent to the Asylums of the Metropolitan Asylums Board. These cases, therefore, may be practically left out of account, although it may be remarked that the relatively few cases of imbecility and idiocy which are admitted are especially prone to die of tuberculosis. More of this class, especially boys, are admitted to Colney Hatch Asylum, and when I made the autopsies there I noticed that death from tuberculosis was very common, and this accords with experience elsewhere.

I am indebted to Dr. Elkins for the following figures from Leavesden Asylum. During the five years (1-1-03 to 31-12-07) 693 deaths occurred, necropsies were made in 657 instances (95 per cent.), and 208 cases had active phthisis at death. This latter figure includes the few cases of tuberculosis which did not come to autopsy. Hence the percentage of cases dying with active phthisis at Leavesden was 30 per cent. Dr. Elkins has been very interested in the subject of tuberculosis, and has done valuable work in connection therewith; he has made a special effort to ascertain the existence of tubercle during life and *post mortem*, consequently it may be assumed that this figure represents accurately the proportion of deaths with active tuberculosis. It is therefore comparable with the Claybury figures. It will be observed that the proportion of Leavesden to Claybury is 3 to 2; it might be asserted that this is due to the fact that we are comparing an old asylum with a new asylum, but it has been shown that the old London County Asylums—Hanwell, Colney Hatch—have certainly not a higher incidence than Claybury—a relatively new asylum. The increased death-rate with active tuberculosis must therefore be associated with the class of patient at Leavesden, and the fact that imbeciles, idiots, and incurable cases of insanity, which make up the bulk of the population of Leavesden Asylum and the other institutions under the Metropolitan Asylums Board, should die so frequently with signs of active phthisis accords with our experience and with the statistics of the Prussian Blue Books.

The remainder of the cases may be grouped into paralytics and non-paralytics; the diagnosis of the form of mental disease in the latter was symptomatic and does not therefore permit of systematic classification, yet the large number of cases diagnosed as melancholia clearly indicates a marked association of mental depression and tuberculosis. If we adopt Kraepelin's classification and only include under melancholia involutional forms of mental depression, then clearly the cases of melancholia would be comparatively much less numerous. As mentioned on page 79 it is the insanity beginning in adolescence (*dementia præcox*) which is so frequently associated with tubercle, and it is quite probable that in

these patients the seeds of tubercle had not been sown on admission to the asylum; as the mental symptoms progress the liability to infection increases, but does this necessarily imply that they would be more likely to perish from tubercle or perish in a shorter time if they were brought to an asylum than if they remained at home. If tubercle is the infective disease that it is believed to be by many authorities then the bringing of feeble-minded into asylums and keeping them there till they die should be a potent influence in diminishing the spread of tuberculosis as well as of insanity, not, I believe, so much by removing a source of infection by tubercular micro-organisms, although it would so operate, but by preventing such weeds propagating their like, and transmitting to future generations mentally and physically unsound stocks which would infect healthy stocks. Segregation of the feeble-minded in colonies and institutions before they have arrived at the reproductive period of life would in the end turn out a national economic as well as a hygienic measure, and would diminish pauperism, crime, insanity, and tuberculosis. We know that prostitutes in our large cities are nearly always sterile from venereal disease; otherwise it would be positively appalling to think of the number of illegitimate children defective in mind and body that the State would have to maintain if in large towns women who led immoral lives had numerous children, as so frequently happens in country villages.

*Occupation.*—I have ascertained the occupation of the patients dying with active phthisis at Claybury during the past ten years:—

MALES.					
Labourers	...	56	Fish Porters	...	3
Clerks	...	18	Coal Porters	...	3
Carpenters	...	11	Coachmen	...	3
Soldiers	...	7	Shoemakers	...	3
Painters	...	4	Grocers	...	2
Plumbers	...	4	Policemen	...	2
Engineers	...	4	Hawkers	...	2
Sailors	...	3	Cooks	...	2
Upholsterers	...	3	Tailors	...	2
Printers	...	3	French Polishers	...	2
			Railway Porters	...	2
			Hatters	...	2
			Errand Boys	...	2
			Instrument Makers	...	2
			Unknown	...	5
			No occupation	...	10
			Total	...	160

(The remaining 41 cases had each different occupations.)

These figures do not show much regarding the influence of occupation on the incidence of phthisis, as in a pauper asylum one would expect the main proportion of the patients to be of the labouring and poorer class.

The females, however, show more interesting figures:—

## FEMALES.

Housewives	47	Laundrymaids	3	Brush Workers	2
Servants	27	Hawkers	3	Factory Hands	2
Charwomen	17	Nurses	3	Barmaids	2
Needlewomen	9	Machinists	3	Unknown	4
Housekeepers	6	Fur Hands	2	No occupation	58
Dressmakers	6	Bootmakers	2		
Cooks	3	Bookfolders	2	Total	201

(The remaining 14 cases had each different occupations.)

It will be observed that more than 25 per cent. of the cases occurred among women who were registered as of no occupation.\* As the great majority of these women are of the pauper class and must do some work or have some occupation in order to obtain the necessities of life, and bearing in mind what was said concerning the female general paralytic, it seems highly probable that a considerable number of them may belong to the unfortunate class that are obliged to obtain their living by prostitution. A number of feeble-minded females, either by choice or necessity (often both causes combined), take to this mode of living, and in them all the conditions are favourable for the development of tuberculosis. A certain number of young women who break down mentally in the early period of adolescence or who are feeble-minded from birth, and have always lived at home without any occupation, form a part, but I think it is probable the smaller part, of this 25 per cent. of tuberculous women with no occupation.

## III.—PROPHYLAXIS.

Since Koch, at the Tuberculosis Congress held in London in 1901, affirmed that the main cause for tuberculosis was its communicability from diseased to healthy persons by the expectoration containing the tubercle bacilli, there has been a widespread movement in all civilised countries to combat the spread of the disease by this means.

The death-rate from tuberculosis in England, however, had shown a remarkable decline before science even had discovered the cause of the disease. Professor Brouardel, in his address at the same Congress, said: "You have diminished mortality in England from tuberculosis by 40 per cent.," and he attributed this decline to the numerous Acts of Parliament

\* The large number of women in London that earn their living by prostitution are largely the victims of venereal disease and are for the most part the subjects of alcoholism. All these conditions tend to lower the vital resistance against tubercular infection. I do not find the occupation of prostitute mentioned in the official asylum records, yet there must be a great number of such women admitted to the asylums.

and measures promoted by private individuals to render more salubrious the dwellings of the poor and the conditions under which they live and carry on their occupations in factories, mines and workshops throughout the kingdom:—

“Unhealthy dwellings cause other disasters. Dark and crowded as they are, cleanliness is difficult, if not impossible, to preserve; they are not pleasant to pass their time in, and the workman stays in his home as little as possible; he eats there and sleeps there, but the rest of his time is spent in the public-house. J. Simon was right in saying the wretched lodging is the purveyor of the public-house, and we can add to it that the public-house is the purveyor of tuberculosis. In fact alcoholism is a most potent factor in the production of tuberculosis.”

Not only does alcohol *per se* lower resistance, but it is the most fruitful cause of pauperism and all its attendant evils of unhealthy, overcrowded dwellings with insufficient air and light; moreover, money expended by the poor in drink means usually insufficiency of nutritious food, thus a combination of devitalising conditions are brought about which favour both soil and seed in the development of tuberculosis. It has already been remarked that it is a general opinion founded upon statistics that the high death-rate from tuberculosis among the insane as compared with the outside public was in great measure due to the asylums and not the patients—in fact, that a large proportion of the cases of tuberculosis are therefore preventable. If this be so it is our bounden duty to adopt all necessary prophylactic measures (having due regard to economy) to diminish this death-rate from preventable causes.

In all measures which may be adopted outside of asylums for the prevention of tuberculosis it is necessary to remember that tuberculosis is not an infectious disease in the sense of diphtheria, scarlet fever, measles, typhoid; indeed, it is probably not so infectious as pneumonia, and it is well to take heed to the warning of Sir Hugh Beevor, who has made a special study of this subject especially in relation to rural phthisis. He drew attention to the remarkable constancy which obtained year by year in the death-rate from pulmonary tuberculosis in the rural districts of Norfolk, where the occupation and population (at ages from 25 to 45) had remained stationary for 30 years.

He further states:—

“No, we must proceed in the interests of all by education and attention to the wants of the people in food and in air, and we shall see the successes of the past excelled by the higher successes of the future. I earnestly hope that the medical profession at large will not encourage the public to avoid their tuberculous fellow creatures. Such a course will not, in my opinion, diminish the amount of tubercle. It will, however, infallibly swell the ranks of the unemployed, it will depress the phthisical wage-earner's spirits, it will

empty his pockets, and ultimately, by want and distress, reduce his family to that condition of low vitality which the tubercle bacillus requires for a successful invasion."

Dr. Haldane informs me of a fact which is also of importance in showing that the *soil* is even more important than the *seed*. Investigation in which he was recently engaged on behalf of the Home Office showed that among Cornish miners at and beyond middle life the death-rate from tubercular phthisis is enormously increased in consequence of the stone dust which they have inhaled during many years of work. Although nearly all these men die at home, and with every chance of spreading infection, the local death registers show no excess of death among the wives and children of miners, and the death-rate from phthisis among young miners is exceptionally low.

Dr. Bulstrode, in his valuable report, comes to the following conclusions: "The facts here set forth may perhaps be regarded as pointing to the conclusion that tuberculosis is not a disease which can be reasonably grouped as regards personal infectiousness with the acute exanthemata such as smallpox and typhus fever; and this position, if accepted, should involve a material difference in administrative action. Tuberculosis may, perhaps, be best viewed as occupying a distinct and separate position from the exanthemata, and, as regards its duration and low degree of infectivity, meriting a class to itself."

Practically speaking, there are two portals of entry of the specific organism, viz., the *respiratory tract* (possibly the tonsils) and the *intestinal tract*, and in respect to this important question it is desirable to refer again to Koch's memorable address, when he affirmed that the bacillus of human tuberculosis was incapable of producing tuberculosis in bovines, and that bovine tuberculosis was practically incapable of being transmitted to man; therefore the danger of contracting phthisis from the meat or milk of tuberculous cattle need not be guarded against. This dictum of Koch was not accepted by the majority of authorities on the subject. It is now generally admitted that there is a practical identity of human and bovine tuberculosis. Koch states his views thus: "In by far the majority of cases of tuberculosis the disease has its seat in the lungs and has also begun there; from this fact it is justly concluded that the germs of the disease must have got into the lungs by inhalation. We know with certainty that they get into the air with the sputum of consumptive patients; the sputum of consumptive people, then, is to be regarded as the main source of the infection of tuberculosis." On this point he says, "I suppose we are all agreed."

Sir William Whitla, in his admirable Cavendish lectures, adverting to this statement of Koch, says:—

“Many facts, some of them of rather a startling nature, have been brought to light since the above words were printed a few years ago, and though it is no part of my present purpose to attempt to prove that phthisis may not sometimes be produced in this manner, it shall be my endeavour to show that the results of recent experiment should induce us to conclude that the intestinal route plays a far more important rôle in the production of human pulmonary tuberculosis than has been hitherto recognised.”

In support of this view Sir William Whitla refers to the results of a number of recent investigations as well as those which he conducted in conjunction with Professor Symmers, and he states:—

“These observers, however, reject Von Behring’s affirmation that adult phthisis is always the result of an intestinal infection contracted in infancy, since their experiments have demonstrated how easily and simply intestinal absorption causes pulmonary tuberculosis in adult animals. Then step by step the statements regarding the specific differences between the human and bovine bacillus, and those made about the impossibility of infecting bovines with human tubercle, as well as the erroneous views regarding the part played by inhalation, have been disproved and the way finally opened up for a clear appreciation of the intestinal origin of human phthisis through the demonstration afforded by experimental researches carried out on the lower animals.”

As there can be no doubt that experiment and observation have indubitably proved that the milk of infected cows can produce tubercular infection of the human subject; and seeing that there is a widespread occurrence of the disease in bovines from which we derive our milk supply and a considerable proportion of meat consumed, it is obvious that one of the most important steps to be taken in regard to prophylaxis is to stamp out the disease in these animals or to adopt such measures as may ensure the public against infection from this source. It has been already said that there are two main portals of entry—the lungs and the intestines; and practically it may be said that there are two sources of infection: (1) By inhalation (*a*) of dried dust containing the tubercle bacilli mainly derived from the expectoration of patients in the second and third stages of pulmonary phthisis; (*b*) by the inhalation of particles of moisture containing the bacilli expelled from the respiratory passages of tuberculous patients, especially upon coughing. (2) The bacillus may enter the body with the food and, since experiment has shown that it is not necessarily destroyed by the gastric juice, it can enter the body by the intestine and leave no signs there of its passage into the lymphatic system; the bacilli coming from the milk or butter, or uncooked flesh of

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infected animals, can produce primary tuberculosis in the lungs. Sir Wm. Whitla remarks:—

“That dosage is everything in the consideration of phthisis. Probably a very small proportion of those infected by the bacillus of tubercle develop the clinical symptoms of the disease, and it is here that the natural resistance as manifested in the form of heredity comes into consideration; when the dose is large probably no human can escape . . .

“The number of tubercle bacilli discharged daily in the sputum of a patient in advanced phthisis has been said to be as great as the number of human beings on the earth. The modest estimate mentioned by Cornet may be taken as nearer the truth, viz., that 7,200,000,000 may be daily thrown off in the sputum from a single individual.

“Even when we consider that a large proportion of these bacilli are dead the numbers are so colossal as to defy realisation, and we must be driven to the conclusion that the bacillus of tubercle is ubiquitous. Every individual draws it into his upper air passages in the form of dust, swallows it in milk, and probably injects it in infinitesimal amounts in almost every form of food which has been long exposed to the city atmosphere. Were there not some powerful phagocytic and other mechanism for dealing with these minute doses of the tubercle bacillus within the human healthy body, there probably would be few, if any, of us left to study or discuss the tuberculosis problem.”

There can be no doubt that, although the tubercle bacillus is ubiquitous, and likely in spite of all prophylactic measures to remain so, yet that if dosage is of such importance in the production of the disease, then all measures which tend to diminish the number of tubercle bacilli which the asylum inmates must perforce take into the body, either by inhalation or by ingestion with food, will certainly tend to reduce the death rate from that disease in asylums.

We have seen that in successive years following notification an increasing number of tuberculous cases were discovered, and in the majority of instances segregated. This would tend undoubtedly to a diminution of the dosage of the inmates who were healthy or free from active disease. In this respect notification therefore has been a prophylactic measure of importance.

It might be asserted that there is no certain evidence that dosage plays any part in the question of incidence of tuberculosis in attendants and officials in lunatic asylums. But even if this be admitted, which is doubtful, comparisons cannot be drawn between the relative effects of dosage upon people healthy in mind and body and the insane inmates who for the most part are physically feeble and of low vital resistance. Consequently, if we admit the principle of the dependence of infection upon the daily dosage, the most important prophylactic measure resolves itself into the question of early diagnosis of active pulmonary phthisis and how it may be successfully attained. On p. 80 we have seen that a large proportion of the cases (25 per cent.) are not diagnosed during life.

Whether the portal of entry be either the lungs or intestines, there can be no question that a high percentage of unrecognised tuberculous patients with active disease must cause a sowing of the seeds broadcast; and the most important prophylactic measure to reduce the relative amount of dosage of bacilli rests with the medical officers of asylums, who by systematic examination of suspected patients would diminish greatly the liability to large dosage by the early recognition of active disease and by adopting the necessary prophylactic measures.

The first stage is the most important, for it is then intervention is of real use; again, by curing the tuberculosis there is hope of curing the mental affection; for the same cause may be at the root of each affection and reciprocal interaction of the mental disease and the tuberculosis tends to the production of a vicious circle, which can only end in death. \*The frequency with which one meets with tubercular ulceration of the intestines is due to the fact that the insane swallow their expectoration; of course, this tends to destroy any hope of recovery, and I think every endeavour should be made on the part of attendants and nurses to encourage patients to spit into properly provided receptacles, even though it may cause the nurses and attendants trouble to destroy the contents and cleanse the vessels daily.

It is probable the air in the wards and dormitories of the London County Asylums is not more contaminated by tuberculous organisms than the homes of the people who are the inmates. Some years ago, when Dr. Durham and I were investigating dysentery, Dr. Durham took some of the dust of a ventilator flue of one of the large day rooms, and inoculated a guinea pig without any result. A single experiment is of little value, and I should have liked to have made an extended series of observations upon this important question; but, although there are hundreds of guinea pigs kept for the amusement of the patients, my laboratory not being licensed, I am unable to utilise these for purposes which might be of much more use to the unfortunate inmates.

I am inclined to think that there is a greater danger of conveyance of tubercle bacilli from an infected individual to a non-infected individual by the fine particles of moisture expelled in coughing than by the dust of dried sputum. I have not observed much evidence of patients spitting on the floors when I have visited the day rooms and dormitories of the London County Asylums. As regards personal cleanliness the inmates of asylums are frequently defective in their habits, and their clothes are often soiled by faecal matter; but apart from the fact that there is

\* The tubercle bacilli were found by Dr. Candler in the stools of a patient who was supposed to be suffering with dysentery, and he is at present engaged in a research with the view of ascertaining if the examination of the stools of doubtful tuberculous cases would afford an additional means of diagnosis.

the disadvantage of large numbers collected together, the personal cleanliness and hygienic conditions are of a higher standard than the generality have been accustomed to. Moreover, the quantity and quality of the food is better than the majority of people of the same class obtain outside the asylum.

Nevertheless, in my view, the facts and statistics tend to show that active tuberculosis runs a more rapid course in the insane than the sane, and this is mainly owing to an inherent *low vital resistance* and the greater danger of auto-infection and associated invasion by *septic and pyogenic organisms*.

Various prophylactic measures have been adopted at all the London County Asylums to prevent infection and to improve the vital resistance of tuberculous patients. The following summary of the precautions adopted has been prepared from the information kindly supplied by the superintendents of the various asylums:—

*Re milk supply.*—All cows are submitted to the tuberculin test and sent back to the vendor if they are found to react. In many asylums it is apparently the custom to apply the test periodically. The risk of infection from tuberculous milk is greatly diminished in the case of the inmates of the London County Asylums as compared with the outside population, for whereas in the former case the milk supply is carefully superintended, in the latter case, according to the Medical Officer of Health for the City of London, “practically no precautions are taken by either the farmers or the wholesale dealers in London to ensure that the milk for which they are responsible is not a vehicle for the conveyance of tuberculosis.” This is evidenced by the fact that during the first three months’ inspection of milk samples (July—September, 1908) by the London County Council 23 per cent. were found to be tuberculous, and from the following October to January, 285 samples were examined and 7·7 per cent. were found to be tuberculous.

It would be interesting to know what percentage of the samples of butter sold in London contained tubercle bacilli, as this is a staple article of food, especially for the poorer classes, and, as the greater part of the quantity consumed is not subjected to any process of cooking, it may be a fruitful source of infection.

Dr. Moody states, referring to the tests:—

“These may or may not be of value, but I can say that before the test was applied before purchase, we often had found the carcasses on slaughter so tuberculous that they were condemned as unfit for food, whereas this is now quite the exception.”

At Colney Hatch Asylum the tuberculin test is now not applied, but the

milk is submitted to the Council's chemist for examination. Milk from the farm is sterilised.

*Re therapy, diet, and sanitation:*—There is apparently no routine therapy or dietary for tuberculous patients. Each case is individually catered for with such extras of milk, beef tea, dripping fat, cod liver oil and malt, creosote, etc., as may be indicated. The possibility of the entrance of tuberculous organisms into the body by butter made from the milk of tuberculous cows does not arise, as margarine is used as a substitute.

The ordinary methods of sanitation are practised. Spitting cups are washed out frequently with disinfectants, sputum is wiped up from the floors with rags, which are immediately burnt. The side rooms inhabited by tuberculous patients are disinfected, and at one asylum Sanitas lamps are burnt in the phthisical wards.

*Re isolation.*—All diagnosed tuberculous cases are isolated as far as the mental condition of the patient and the construction of the asylum will allow:—

*Banstead Asylum:*—

"Male cases collected in Ward 8, a detached bungalow; females, in one special ward."

*Bexley Asylum:*—

"All patients suffering from tuberculosis are collected together and, as far as possible, are isolated, the males in the East Villa and the females in H 1 ward (*vide* Plate I.). They are given open-air treatment, and if the patients are confined to bed, the beds are placed in verandahs."

*Cane Hill Asylum:*—

"Our tuberculous patients, with few exceptions, are placed in J 1 and J 2 wards, female division, and G 2 ward, male division, to which large verandahs have been attached on my recommendation. In these wards we are able to treat the patients largely in the open-air with decidedly beneficial results."

*Claybury Asylum:*—

The tuberculous cases are collected, as far as the mental condition will allow, in special wards."

*Colney Hatch Asylum:*—

"All tuberculous patients on the female side of the Asylum are at present collected in Ward E 3; they will shortly be removed to the new infirmary (*vide* Plate II.) for tuberculous cases, which is provided with verandahs. On the male side the greater number of the tuberculous patients are collected in Ward C 5, and it is in contemplation to provide a verandah in connection with it. The remainder of the cases are kept in single rooms."

*Hanwell Asylum:*—

"Unfortunately we have no means here of carrying out absolutely the isolation of tuberculous patients. As far as possible we place all such patients in single rooms, but owing to the necessarily imperfect ventilation of these

rooms (due largely to their size and the absence of fireplaces) I am in considerable doubt as to the wisdom of this proceeding. We have no special means of carrying out the open air treatment. Such tuberculous patients whose mental and physical condition will allow are warded in infirmary wards, from which there is easy access to a court, and they are permitted to spend practically the whole day out in this court when the weather is favourable."

*Horton Asylum:—*

"All patients showing active signs of tuberculosis are housed chiefly in infirmary A on the female side, and infirmary I on the male side. Attached to these two wards are large verandahs where treatment, as far as possible, is undertaken in the open air (*vide* Plate III.). A few of the more excited ones, however, have at times to be kept in infirmary B on the female side, and infirmary 2 on the male side."

*Long Grove Asylum:—*

"All tuberculous patients are isolated in one ward on each side of the building. This ward has two dormitories and a number of single rooms besides the usual day-room and dining-room. All the active cases of tubercle are placed in one of these dormitories; certain of them whose habits of spitting are very marked or for other special reasons, are placed in single rooms. Practically all of these cases who are not up and about spend the whole of each day from either before or just after breakfast until sunset in beds under a wide glass verandah built out along one side of this particular dormitory, and other tubercular cases sit there and also have the use of the garden."

*Horton Manor Asylum:—*

"Tuberculous cases are collected together, as far as possible, in special wards."

*The Epileptic Colony:—*

"Very few cases of tubercle occur; they are treated in the Infirmary Villa, the verandah of which is suitable for open-air treatment in the daytime."

It will be observed that at all the asylums isolation of patients suffering with active tuberculosis is practised as far as the mental condition of the patient and the construction of the asylum will allow. At Colney Hatch a special isolation hospital for tuberculous patients (Plate II.) is in construction, and it will be interesting to see in the future how far the incidence of active tuberculosis diminishes in that asylum and how far that institution will compare favourably with another old asylum like Hanwell, in which there is no special provision for isolation or open-air treatment. The admirable verandah arrangements at Bexley, Horton, Long Grove, and Cane Hill, to my mind, are economical and fulfil all the purposes required.

The great decline in the tuberculosis death-rate among the outside population which has taken place during the last 30 years is undoubtedly due to the improvement of the general social conditions of the people, *e.g.*, the better housing of the poor, the improvement in the conditions of light and ventilation in workshop and factory, combined with cheaper

food and the fall in the drink-bill. Doubtless the death-rate from this disease will steadily go on falling for the same reason that every year sees a progressive improvement in the social conditions of the mass of the people ; and a steady fall in the death-rate from the time tuberculosis is regarded as an infectious disease and made notifiable, may be ascribed wholly but erroneously to the great diminution of dosage—that is, the dissemination of the seed—by this special measure. But if tuberculosis is to be a notifiable disease, why not syphilis? Certainly, the evidence of conveyance of the disease from one individual to another by contact and cohabitation is very weak in the former as compared with the latter.

The more phthisis can be treated in the early curable state the less will be the chance of there being a focus of discharge of tuberculous organisms.

This is a matter of diagnosis, and it might be desirable to adopt in our asylums even more systematic attempts to discover early cases on admission, or shortly after admission, for it appears to me this is the very essence of the question of prophylaxis.

#### SUMMARY.

1. The evidence adduced does not support the contention that infection is one of the *strongest* causative elements in the prevalence of tuberculosis in the London County Asylums ; still less does it support the view that the causes of tuberculosis *inhere* in the Asylums themselves and not in the character of the patients sent to them.

2. Notification during five years from all the London County Asylums does not show any ward incidence comparable with that shown by the notification of dysentery during the same period ; therefore if tuberculosis is communicable, it cannot be regarded as an infectious disease in the same sense as dysentery, small pox, scarlet fever, etc.

3. The average proportion of living patients reported as tuberculous is 20 per 1,000 inmates of the London County Asylums, but the incidence of reported cases shows very considerable variations, the lowest being Cane Hill, 10·6, and the highest Claybury, 40·3. The personal equation must largely contribute to these wide differences.

4. Association with mental disease of the cases reported during life indicates that young subjects suffering from melancholia, dementia præcox, and imbecility are especially prone to the disease.

5. Post-mortem statistics confirm this correlation, but in addition show that a large number of general paralytics die with recent active tuberculosis which is not diagnosed during life ; this is especially the case in regard to female general paralytics, for which fact reasons are given.

6. In 14·8 per cent. of the autopsies made at the London County Asylums during the past five years, active phthisis was found. Again, a great variation in the returns from the various Asylums was noticeable, for which the personal equation must be held largely responsible.

7. It cannot be shown that the variation in the incidence of tuberculosis in the various London County Asylums depends in any measure upon the class of patient received, the parish areas from which they are drawn, the construction and age of the Asylum, or the dietary or treatment. Cane Hill Asylum, situated on a high chalk down, has a comparatively lower death-rate and a lower tuberculosis death-rate than any of the other London County Asylums. The relatively higher death-rate from tuberculosis at Claybury may be explained to some extent by the fact that the necropsies are made by a skilled pathologist, but it might be attributed to the clay soil and cold damp climatic conditions, although the total death-rate is lower than at most of the other Asylums.

8. A comparison of the phthisis death-rate for 1907 at the several age periods per sane living in London, and per 1,000 of the total living insane population (18,872) resident in the London County Asylums show that the mortality from phthisis among the insane is highest at a much earlier age period than among the sane. At the age period 45-55, when it reaches its maximum among the sane, it is a question whether the incidence among the insane is much greater than among the sane pauper population.

9. The comparison also shows that the death-rate from phthisis for the insane between the ages of 15-35 is about 15 times that for the sane for the same age period. Allowance, however, must be made for the fact that the majority of the inmates of the Asylums belong to the poorest classes.

10. The Jewish population at Colney Hatch (mainly aliens) show a higher death-rate (25·7 per cent. of total deaths) from tuberculosis than the Christians, for which fact reasons are given.

11. Evidence is not forthcoming to prove that the staff in the London County Asylums contract tuberculosis from the patients.

12. During the past ten years 1,982 necropsies were made at Claybury Asylum by skilled pathologists, and active phthisis was found in 416 cases (20·9 per cent.). Tuberculous ulceration of the intestines was found in 73 males (36·3 per cent.) and 115 females (53·4 per cent.) of the cases dying with active tuberculosis. Twenty-five per cent. of the deaths with active phthisis occurred within one year of admission, and practically 70 per cent. within five years of admission.

13. The *post-mortem* statistics for the past six years show that 51·6 per cent. of all the patients dying exhibited either obsolescent or active

tuberculosis or both. It was inferred from the *post-mortem* examination that not more than 10 per cent. of the cases with active phthisis at autopsy could have acquired the disease in the Asylum.

14. Infection with the disease depends upon dosage and resistance.

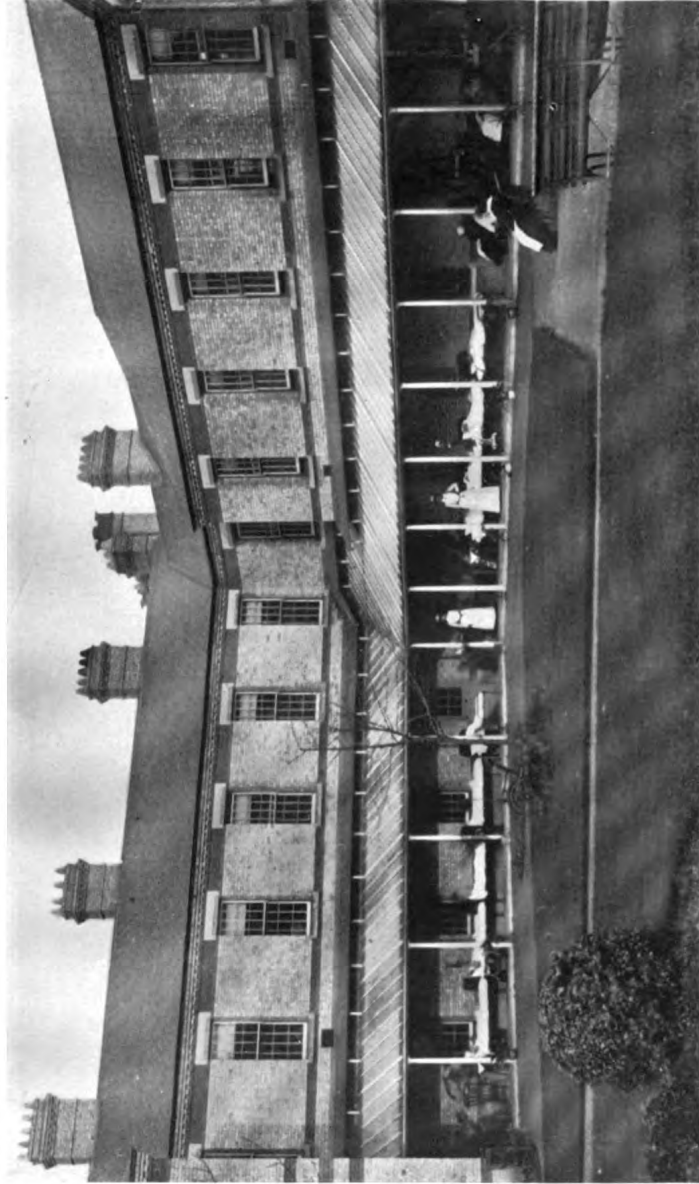
15. The prophylactic measures for the prevention of tuberculosis are good in the London County Asylums as regards milk, food, personal cleanliness, ventilation, clothing, warmth, and exercise in the open air, and the liability to infection from preventable causes is less than in the houses from which the majority of the insane are taken. The only further prophylactic measures consistent with proper and due economy appear to be (1) the *earlier and more frequent* diagnosis of active phthisis with a view to isolation and treatment, (2) the adoption of the verandah system of open-air treatment at all the Asylums, and (3) the encouragement of patients suffering with phthisis to expectorate into proper receptacles and thus possibly diminish the amount of intestinal tuberculous ulceration caused by autoinfection.

I am indebted to the medical superintendents of the various Asylums for much valuable information and the illustrations shown in Plates I. and III.; also to Mr. Clifford Smith for the plans of the new hospital at Colney Hatch (Plate II.).

In conclusion, I wish to thank Dr. Bulstrode for his valuable advice and for kindly looking through this paper. Also I desire to acknowledge the help I have received from his valuable reports for the Local Government Board, "Sanatoria for Consumption and certain other Aspects of the Tuberculosis Question." Moreover, I wish to acknowledge the invaluable aid I have received from my assistant, Mr. Sydney Mann, in keeping the records for the past five years and preparing the statistics therefrom.



PLATE I.



H 1 Ward, Female Side, at Bexley Asylum, showing verandahs for open-air treatment of Tuberculosis.

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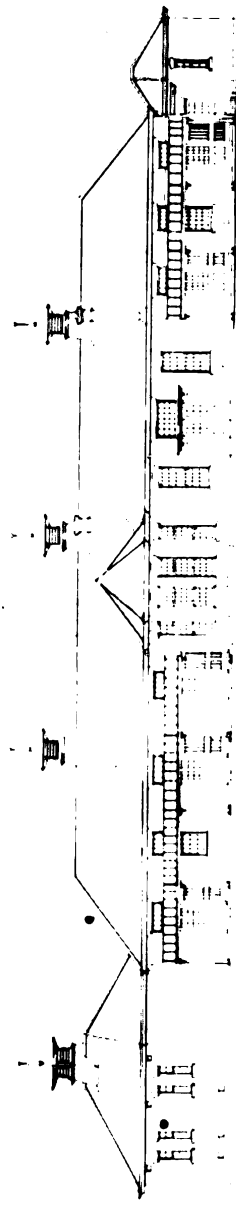
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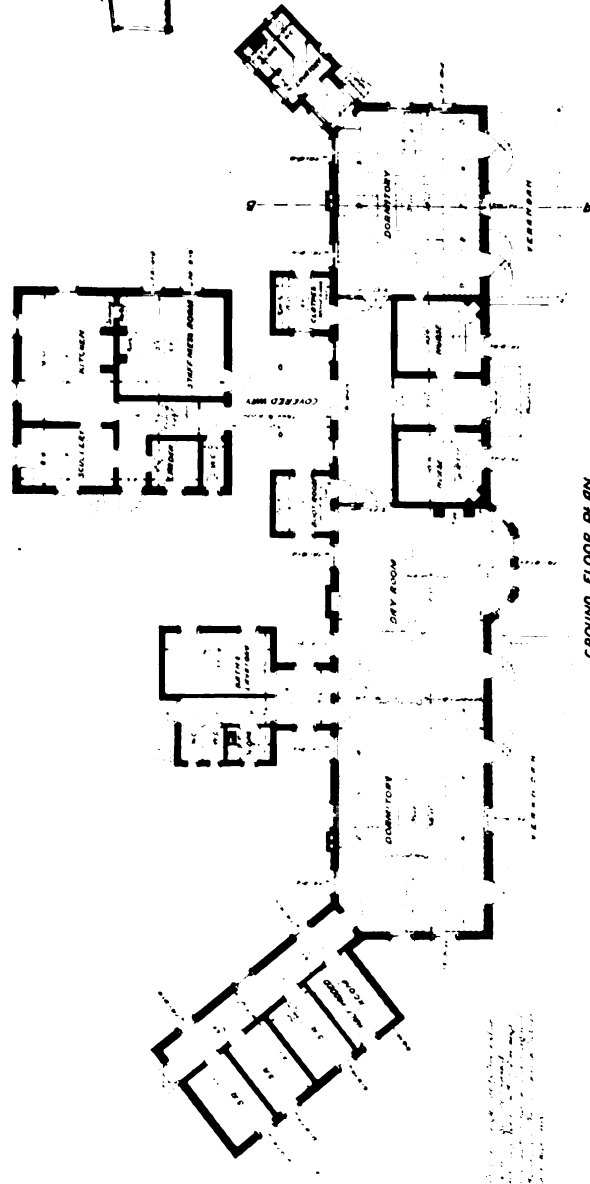
# COLNEY HATCH ASYLUM WARD FOR PHTHISICAL PATIENTS

SCALE EIGHT FEET TO ONE INCH

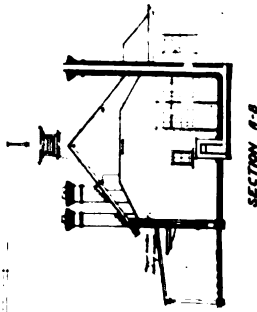
DRAWING NO 966



SOUTH ELEVATION



GROUND FLOOR PLAN



SECTION A-B

J. S. C. (Architect) & J. S. C.  
ASYLUM ENGINEER  
DECEMBER 1901

The Hospital is for 24 Female Patients. To ensure a full supply of air in the wards and dormitories, there are hoppers above each ordinary window, which can be arranged to ventilate the upper part of the rooms when the windows are shut. The dormitories are heated by central stoves, and the single rooms by low pressure steam. Glass covered verandahs are attached.



PLATE III.



Female Infirmary at Horton Asylum, showing verandah for open-air treatment of Tuberculosis.



## EXAMINATION OF THE NERVOUS SYSTEM IN A CASE OF CHRONIC LEAD ENCEPHALITIS.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

With Clinical Notes by FREDK. H. STEWART, M.D., Senior Assistant  
Medical Officer, Kent County Asylum.

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J. D., æt. 44, married, coach-painter, said to be an epileptic, was admitted under my care on November 18th, 1907.

*Family history.*—No insanity or alcoholism traceable. Father died from pulmonary tuberculosis, æt. 44. Mother alive, æt. 79. Two brothers and five sisters alive and apparently healthy. Paternal and maternal grandmothers and grandfathers lived to an advanced age.

*Personal history.*—Has been a painter since he was a boy. Never acquired syphilis. Used to drink heavily at times. Is said to have been treated for "enlargement of the liver" three years ago. Married about 16 years ago to a healthy young widow, 4-para. All her children likewise healthy. She states that she never conceived by him, although she is now still within the child-bearing age.

While at his work, painting a motor-car, early in July, 1907, he suddenly became unconscious, owing to the onset of a convulsion, described by a medical eye-witness, as epileptiform in type, and diagnosed by him, as due to plumbism.

For some time previously he had suffered much from agonising colic and obstinate constipation. He recovered from the convulsion, and was able to resume his work in a few days. Then it was noticed that he broke down at his work, time after time, and if he attempted to pull himself together by alcoholic indulgence, even in very small quantities, it "made a fool of him." His fellow-workmen noticed this, as previously he was able to carry a decent "load" with apparent impunity. He was admitted into a union infirmary on two later occasions, viz., August 14th and September 2nd, 1907, treated there for alcoholism, and duly discharged recovered.

*Present illness.*—Began by a somewhat sudden onset on November 13th, 1907. He was observed to have a wild appearance, incoherent ideas, inability to give a reasonable account of himself, illusions of

sight, wanted to eat his pillow, restless, habits unclean, difficulty in swallowing, pulls his bed about, and looks under the clothes very much. He had not had any alcohol for three to four weeks previous to this date.

*State on admission—General.*—Very weak and tottery. Temperature, 99·8 F., weight 8 stone 7 lbs., height 5 ft. 9 ins.

Marked cachexia, face in lower third looked puffy (*vide* Fig. I.), pupils dilated, equal, but eccentric.

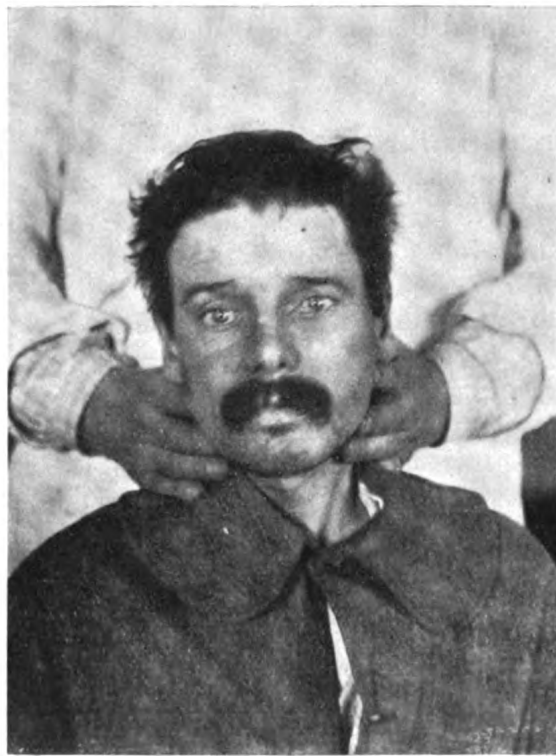


FIG. 1.

Oral sepsis, breath very offensive. An irregular blue line present in gums. This remained after thorough cleansing with cyllin and tooth brush. Two irregular slate-coloured patches also present in mucosa lining lower lip. Palatine conformation rather high and narrow, with tendency to irregularity.

*Mental condition.*—Marked restlessness, appearance excited (*vide* Fig. 1), general clouding of consciousness, disorientation, difficulty in



comprehension. Ideas confused; attention weakened, remitting delirious states. Periods of shouting, apparently coincident with the paroxysms of colic. Rather drowsy, but has short lucid intervals. At night he becomes worse, being very sleepless and continually tries to get out of bed. Is passively resistive, has auditory hallucinations, says he has severe pains in the head, asks to be killed, craves for water, is in a state of morbid fear.

*Physical condition.*—*Decubitus dorsalis*, with both thighs flexed on abdomen and some flexing of trunk generally. Unable to stand alone, hand grip and gait impaired. Bilateral drop-wrist, and extensor paralysis of all the fingers; spills contents of his feeding cup on attempting to lift it towards his mouth. Supinator longus not affected. The reaction of degeneration is present in the paralysed muscles; there are coarse tremors observable chiefly affecting the upper extremities, also irregular fibrillary twitching of the same parts. Staccato articulation.

*Sensory.*—During the lucid periods no marked alteration could be detected in common, thermic, or pain sensibilities. Stereognostic, vibratile and muscular doubtful. He did not wince on deep pressure being made on the paralysed muscles.

*Reflexes.*—The pupils are regular, equal, and of moderate size. They react sluggishly to light and accommodation.

Cremasteric and epigastric diminished. Plantar extensor reflex not obtained. The knee jerk is brisk, especially on the right side, ankle clonus absent, elbow jerk exaggerated, jaw clonus easily elicited.

*Organic.*—Deglutition difficult, can only take liquid nourishment. Respirations laboured (12 per min.). Micturition and defæcation at times are not under control. Enuresis at times.

*Trophic.*—There is marked wasting of muscles in all the interosseous spaces, also of the thenar and hypothenar eminences. Some thickening and contraction of palm, the general voluntary musculature was atonic, and fibrillar contractions were characteristic.

*Vaso-motor.*—Tache cerebrale well marked.

*Fundus oculi.*—Neuro-retinitis present, but unequal in the two eyes. Impairment of vision.

*Heart.*—Impulse beat in nipple line, action increased, but varied with exacerbations of colic. First sound in mitral area impure, no transmitted bruit. Second sound in aortic area accentuated, pulse variable in rate, regular. Radial palpable. Pressure variable, high when colic was severe. The majority of the arteries were thickened.

*Lungs*.—Slight cough. No definite physical signs of disease.

*Abdomen*.—Slight retraction, rigidity, tenderness chiefly on right side and above umbilicus. Testicular atrophy, loss of sensibility on pressure.

*Urine*.—Clear, acid, Sp. Gr. 1.011. Trace of albumen. Lead not tested for.

#### TREATMENT AND PROGRESS.

Owing to the difficulty in swallowing he was given only fluid nourishment from a feeding cup. It consisted of milk and albumen water in amounts equal to  $\bar{3}$  iv. three-hourly. The extreme thirst was also allayed by enemata of  $\bar{5}$  xx. normal saline solution almost daily. His bowels were kept open daily with white mixture  $\bar{3}$  ss. given at 7 a.m. I occasionally varied this with confection of sulphur in  $\bar{3}$  jss. doses. He was also given a mixture containing potassium iodide, gr. v., thrice daily. The colic and general restlessness were treated by warm baths of half an hour's duration morning and evening. At night a hypodermic of morphine sulph., gr.  $\frac{1}{2}$ , was substituted when necessary.

November 18.—Night report: Two hours' sleep, restless, noisy, continually tries to get out of bed, auditory hallucinations acute, resistive, very confused ideas, wet.

November 19.—Day: Drowsy, lies in bed better, very thirsty, wet and dirty. Saline enema and baths given.

Night: Three hours' sleep, similar to previous night, thirst. Temperature normal.

November 20.—Day: Colic severe, restless, very confused ideas, thirst. Morphine gr.  $\frac{1}{2}$  hypod. Requires feeding with spoon. Warm baths.

Night: One hour's sleep, troublesome to keep in bed.

November 21.—Day: Taken three pints milk with difficulty, short lucid intervals. I frequently conversed with him during these lucid times, and his conversation was rational and well sustained. To my mind the contrast to his usual condition was marked.

Night: No sleep. Morphine gr.  $\frac{1}{2}$  hypod. Colic severe.

November 22.—Day: Similar to previous day.

Night: Weaker, no sleep, unable to get out of bed now, wet.

November 23.—Day: Very confused to-day, articulates with difficulty, soap and water enema at 11.30 a.m., motion light yellow in colour. Two pints of milk. Morphine gr.  $\frac{1}{2}$ .

Night: Slept from 8 p.m. till 3 a.m. Involuntary evacuations. Very weak.

November 24.—Day: Colic less severe, no mental improvement, unable to help himself. Saline *per rectum*, one pint.

Night: Slept eight hours, quieter.

November 25.—Day: Sight noticed to be very bad, has much difficulty in swallowing even liquids, bowels relaxed, motions light yellow.

Night: Slept from 11 p.m. till 4 a.m. Respirations eight per minute.

November 26 and 27.—In padded room owing to falling about, from general debility and tendency to injure himself. Tube fed for first time.

November 28 and 29.—Unable to swallow now; looks like the final stage of general paralysis, emaciation, incoherent jargon. Much mental reduction evident.

November 30.—Evidences of bronchitis present to-day. Saline enema alone given. Very low.

December 1.—Died at 6.50 p.m.

*Post-mortem* December 2nd, 1907, at 11 a.m. Room, temperature 52 F.

Very emaciated cadaver, with slight abrasions on forehead, nose and knees.

*Post-mortem* lividity and *rigor mortis* established.

Slight bruising on arms and chest. Small sores on legs and trunk. Pupils dilated. Arcus on both corneæ.

*Scalp*.—Small areas of ecchymosis present, thickness and attachment normal.

*Calvarium*.—Nothing unusual.

*Dura*.—Dry appearance. Non-adherent.

*Pia-Arachnoid*.—Dry, glistening appearance, slight excess of fluid; frost-like opacities along course of vessels over posterior two-thirds of both hemispheres. Slight injection of vessels.

*Brain*.—As a whole firm, weight  $48\frac{3}{4}$  ozs.

*Ventricles*.—Choroid, pale and cystic, no granulations evident.

*Mouth*.—Very septic. Septic bronchitis. A hæmorrhage about the size of a sixpence present at base of epiglottis and left vocal cord.

*Lungs*.—Some septic broncho-pneumonia in early stage, most marked on right side.

*Pericardium*.—Small amount transudate fluid, epicardial "milk spots."

*Heart muscle*.—Markedly striated, bluish colour. Weight of organ  $11\frac{1}{4}$  ozs.

*Ventricles*.—Contracted, pale yellow formations right side, dark clot and very slight hypertrophy left ventricle.

*Valves.*—Competent, a few areas of atheroma at coronary orifices, and also at attachments of mitral cusps.

*Aorta.*—Healthy in upper parts, atheroma near its bifurcation.

*Arteries.*—All more or less thickened.

*Peritoneum.*—Retroperitoneal hæmorrhage in region outside the pancreas. It was recent and of small amount, and had become diffuse in the loose tissue of the mesentery. Mesenteric glands enlarged, indurated and bluish on section. Oesophagus healthy.

*Stomach.*—Much mucous present and about  $\frac{3}{4}$  iv. bilious fluid. Mucosa pinkish.

*Intestines.*—Stained with bile in upper parts, vessels congested, large bowel constricted at irregular intervals.

*Duodenum.*—Contents semi-fluid, and of an orange yellow tint.

*Jejunum and ileum.*—Contents darker.

*Cæcum.*—Mucosa slate-coloured.

*Colon.*—Irregular constrictions, between which were large dark greenish scybalous masses. Rectum empty.

*Liver.*— $47\frac{3}{4}$  ozs. Bluish colour on section, with pale yellow areas. Bile very dark, no calculi. Soft consistency, volume reduced.

*Spleen.*—Surface mottling, usual size and weight.

*Kidneys.*—Little fat around each. Both cirrhotic, capsule adherent to an atrophic granular cortex. Pale in colour. Right  $3\frac{1}{2}$  ozs., left 4 ozs. Pelves healthy, no calculi.

*Bladder.*—Some turbid urine. Mucosa healthy.

*Supra-renal.*—Right medulla cystic, cortex caseous. Left well marked; differentiation between these two parts. Medulla slate colour.

*Muscles.*—Dark in colour. Wasted.

## I. HISTOLOGICAL EXAMINATION.

*Brain and spinal cord.*—Portions of the top of the ascending parietal and frontal convolutions, top of first frontal and the cervical enlargement of the spinal cord and medulla oblongata, were examined by Nissl, polychrome blue, polychrome blue and eosin, and Van Gieson methods for cell changes. Sections of 6-7u were cut and stained by the above methods after the tissues had been hardened in formalin, dehydrated in alcohol, and embedded in paraffin. Portions of the ascending frontal and parietal, cerebellum and the lumbar, dorsal and cervical regions of the spinal cord were chromed, cut in celloidin, and stained by Weigert and Pal methods to display fibre changes and sclerosis. An attempt was made to stain by the Cajal silver method, but except for the display of the neuroglia

cells it was unsuccessful owing to too prolonged action of the formalin. The glia proliferation, however, is extremely well displayed (*vide* Fig. 6, Plate I., and Fig. 2).

The spinal cord was very much damaged in removal, and the sections accordingly are for the most part unsatisfactory. The nerves were curled up, and owing to imperfect methods of labelling could not be identified.

*Cerebral cortex—Lepto-meninges.*—The pia-arachnoid is thickened somewhat; this thickening is due to fibro-blasts and fibres, there is no infiltration with lymphocytes and plasma cells such as is always found in general paralysis. There is a hyaline thickening of the walls of the vessels, both arteries and veins (*vide* Fig. 7, Plate I.).



FIG. 2.

Drawing of a section of the cortex, showing the hyperplasia of the neuroglia cells, stained by Heideinhain hæmotoxylin eosin method. Magnification 750.

*The cortical vessels and perivascular sheaths.*—There is some congestion of the vessels, but the perivascular sheaths of the pia-arachnoid show *no cell infiltration with lymphocytes and plasma cells*. The walls of the vessels, however, are thickened, and, owing to the congestion and cell proliferation and hyaline degenerative thickening of the walls of the small vessels, both capillaries, arteries and veins appear more distinct than in the normal brain; moreover, many of the smallest vessels have ruptured, causing miliary microscopic hæmorrhages into the perivascular sheaths

and into the substance of the brain. Adherent to the vessels are large numbers of *branching hypertrophied glia cells* (*vide* Fig. 6, Plate I., and Fig. 2). Some vessels are affected by the hyaline degeneration more than others.

*The neuroglia.*—The most striking feature about the microscopic appearances of this cerebral cortex is the neuroglia hyperplasia. This proliferation of the branching neuroglia cells is observed not only in the superficies of the cortex, but also throughout the grey and white matter; it is most marked in the superficial and deeper layers of the cortex and out of proportion to the wasting of the neural elements; it appears, therefore, to be a formative hyperplasia resulting from chronic irritation. Besides this hyperplasia of the mesoglia cells there is an abundant proliferation of young neuroglia cells consisting mainly of a nucleus containing a fine chromatin network with a number of delicate nodal points with clear hyaloplasm between. These are seen in little colonies, the result of active proliferation, especially in the deeper structures of the cortex and white matter. They are not in the sheaths of the vessels, but are often seen in the perineuronal spaces. They can be followed in all stages up to the formation of large branching glia cells sending their processes on to the walls of the vessels, where they end in a sort of foot-like expansion. There is a considerable amount of subpial felting indicating that the glia proliferation of the molecular layer is of earlier origin than the remainder of the glia proliferation.

*The cells of the cortex.*—The cells are arranged in columns, and all the layers can be seen, although owing to degenerative changes in the cells, to be presently described, and to a great proliferation of the neuroglia nuclei, the regular arrangement of Meynert's columns so characteristic of a section of normal cortex is not so readily made out, *especially is there a neuroglia proliferation in the polymorph layer and the molecular layer.* Changes in the large Betz cells are most readily seen if present, therefore these structures will be first considered. Some of these cells are paler than natural owing to the fact that there is a more or less considerable diminution of the Nissl substance; also the Nissl pattern is more or less lost and a fine dust of stained particles is seen instead of the tigroid substance (*vide* Fig. 2, Plate I.). Where this is present in the cell it is mainly at the periphery; there is, indeed, a moderate degree of perinuclear chromatolysis in some of the cells such as one generally finds in a case of chronic peripheral neuritis whether due to lead, alcohol or other toxic agency (*vide* Fig. 4, Plate I.). The change is not nearly so pronounced as I have seen in other cases. The dendritic processes in some cells appear to be attenuated and not so well seen as in normal structures. Some of

the cells show an accumulation of yellow pigment in one portion of the cells, but, taken as a whole, these cells do not show marked changes indicative of a profound paralysis of the lower limbs. Glia cells are rarely seen in the perineuronal spaces of the Betz cells; whereas in the subjacent polymorph layer and the superjacent pyramidal layers abundance of neuroglia cells are seen apparently exercising phagocytic functions. A ganglion cell is often seen with one or several neuroglia cells glued to it, so that if the neuroglia cell is a large branching one, it is difficult to make out how much of the cytoplasm belongs to the ganglion cell and how much to the neuroglial cell. The impression one obtains is that the neuroglial cells are devouring the ganglion cells.

The view was put forward by Bevan Lewis that the proliferating glia cells "become the 'phagocytes' or scavengers of the tissue; live, thrive, and multiply upon the degenerating protoplasmic masses of nerve cells and their extensions; and all effete material lying in their neighbourhood is ultimately appropriated to their use." Certainly appearances in these sections tend to support this view. The polychrome-eosin stained sections show this best, because the cytoplasm of the neuroglia cell is stained pink. A striking object is the appearance of the neuroglia cells which are undergoing hyperplasia. The nucleus in some of the cells can be seen to have divided into as many as eight daughter nuclei. Again, one sees the pink cytoplasm of the glial cell with branching processes, and in the concavity of two branches a nucleus with only a thin layer of pink cytoplasm around. These young neuroglia cells can be seen in numbers around decaying or disintegrated pyramidal cells; and it appears in places as if they had taken the place of the ganglion cell. But as I am unable to see these glia cells in any section attacking degenerated large pyramidal cells I am *doubtful* how far one can go in asserting that the appearances are conclusive as to their attacking and devouring the other ganglion cells; for the appearances observed may all be due to proximity of the glia cells undergoing proliferation to smaller and primarily degenerated cells. One thing I can be certain of, and that is, there is no polymorpho-nuclear phagocytosis and no leucocytic infiltration of the tissues, and the products of the degenerated nerve cells have to be removed in some way or other.

*Fibres.*—There is no gross atrophy or degeneration of the fibres of the cortex. The tangential and supra-radial fibres are diminished in number, but this is comparatively to general paralysis only slight. Neither the cerebellum nor the spinal cord at any of the levels examined show any fibre atrophy or degeneration except *possibly a slight* diffuse sclerosis in the crossed pyramidal tracts of the lumbar region.

*Spinal cord and medulla.*—The grey matter of the cervical enlargement shows numbers of hæmorrhages, but I am not sure from the appearance of the sections that this may not be due to artifacts. The ganglion cells of the anterior horn show chronic changes which cannot be associated with this condition. There is a perinuclear chromatolysis of some of the cells indicative of a neuritic condition (*vide* Fig. 1, Plate I.). The vessels of the medulla and spinal cord show hyaline thickening and degeneration. The vessels of the choroid plexus show this change in an especially marked manner. There is no evidence of granulation of the floor of the fourth ventricle, a change which is so especially characteristic of general paralysis. There are some microscopic hæmorrhages in the medulla, of the ninth, tenth, eleventh, and twelfth nuclei. A large number of cells of the medulla oblongata, small as well as large, show more or less and in a variable degree some chronic degenerative changes. The processes are broken off, many of the large cells have more or less lost their incurved outline and become more or less rounded; in many of them the nucleus is eccentric, and in nearly all there is some diminution of the Nissl substance. This diminution in the majority of instances is due to a *perinuclear chromatolysis*. This is fairly well seen in a large number of the cells of the vagus nucleus and glosso-pharyngeal nuclei (*vide* Fig. 5, Plate I.); likewise the nuclei of the funiculus gracilis, and Burdach's column show chromolytic changes. The hypoglossal and sixth nerve nuclei do not show so much chromolytic change. A great many of the cells show a marked excess of yellow pigment. Very few of the cells are absolutely normal, but side by side may be seen grades of chronic change. A few vessels may be seen with lymphocytes in the *lymphatics* (not in the perivascular sheath) of the adventitia of the arteries. No plasma cells, however, were seen. As compared with the cerebral cortex and subjacent white matter the glia proliferation is very inconsiderable.

*Examination of the organs.*—Heart, spleen, kidney, liver, lung and suprarenal gland were examined. The portion of the lung examined showed a condition of pneumonic consolidation going on to grey hepatization. The arteries show fibrotic thickening with hyaline degeneration in all the organs, but most marked in the kidney. There is, moreover, a condition of angio-sclerosis, veins and capillaries as well showing the change.

In the liver there is a fibrotic overgrowth around all the vessels in the portal canal and a fatty infiltration of the liver cells.

The kidneys exhibit well-marked interstitial fibrosis with tubular atrophy; this is especially marked about the region of the looped tubes of Henle, the hyaline fibrotic tissue being in places as abundant as the



epithelial parenchyma. The Bowman capsules are markedly thickened, and the glomerular loop also appears shrunken, and marked hyaline degeneration is apparent. In some of the capsules the vascular loops appear to have been destroyed and replaced by a hyaline purple-stained mass; in some cases there is still evidence of it having been a vascular coil, in others this is quite lost, and there is nothing left but the very much thickened hyaline degenerated capsule and a substance like it which fills the area previously occupied by the glomerular vessels; these are quite numerous. The capsule of the organ is markedly thickened and fibrous, and from it there extends into the kidney substance, dense fibrous bands.

Many of the tubes are denuded of epithelium, in others the epithelium is degenerated. Numbers of the tubes contain casts seen in section and easily recognised by a diffuse dull purple stain. The organ is in a fairly advanced stage of chronic interstitial fibrosis (*vide* Fig. 8, Plate I.).

## II.—CHEMICAL EXAMINATION.

The remainder of the brain (both hemispheres) was dried and incinerated, and then extracted with hot dilute nitric acid after repeated incinerations, and finally extracted once with ammonium acetate solution. The filtrates were collected and evaporated to dryness, and taken up in dilute nitric acid.

No trace of lead present by qualitative or microscopic (Copper Potassium Nitrite Method\*) tests.

*Remarks.*—Two brains from lead workers in the Pottery district were sent to me some time ago from the Hereford County Asylum. Upon microscopic examination, one proved to be a typical case of general paralysis; the other was a case of lead encephalitis with polyneuritis. Both were considered to be general paralysis, but then we know that in former times Korsakow's paralysis was called general paralysis. In the case of polyneuritic psychosis in the lead worker, it was extraordinary how marked was the perinuclear chromatolysis of the giant pyramids, very much the same as in the case reported, but more widespread and extensive. The neuroglia cell proliferation was also marked, and there was a widespread hyaline degeneration of the small vessels (arterio-capillary fibrosis), but there was no perivascular lymphocyte and plasma

\* Evaporate solution to dryness, add a few drops dilute acetic acid. Transfer to microscope slide; add one drop copper acetate solution, one drop sodium acetate solution, and two or three drops saturated potassium nitrate solution; stir with a platinum wire; allow to stand for a few minutes, and examine under microscope. Violet black cubes of  $K_2CuPb(NO_3)_6$  will appear if lead is present in a quantity exceeding 0.00003 mg.

cell infiltration, or any marked atrophy of the superficial layers of pyramids, although there was a neuroglia proliferation. In the case of general paralysis in the lead worker there was marked atrophy of the ganglion cells, distortion of Meynert's columns, dissolution, disintegration, and decay of ganglion cells, increase of vessels and neuroglia cells and fibres, and, as Fig. 9, Plate I., shows, marked perivascular cell infiltration.

In Dr. Stewart's case it is difficult to decide how far the symptoms observed during life, and the changes in the organs noted *post mortem* are due to a single factor—lead, or to the combination of lead, chronic alcoholism, and renal inadequacy with uræmia. We know, however, that chronic lead poisoning may be the single factor in the production of a profound metabolic change and in the establishment of a chronic progressive sclerotic condition of the vascular system, and that this may lead to renal sclerosis and an extensive rise of the blood pressure in the arterial system, which, while being in a measure preservative and compensatory, nevertheless by the continuous hypertension tends to damage the whole arterial system, including that of the central nervous system. The vascular degeneration is due, then, to a chronic toxæmia and hypertension. It is not necessary to assume that symptoms of encephalitis in a lead worker means that there is lead deposited in the brain in small quantities. Dixon Mann has found lead in the brain in chronic lead poisoning, but in several cases which I have examined, including the brain of this patient of Dr. Stewart's, I could not find a trace of lead.

The symptoms, however, can be explained quite well; there is abundant evidence of chronic irritation, viz., thickened membranes, angio-sclerotic changes causing vascular stasis with microscopic hæmorrhages and congestion, and proliferated glia cells (*vide* Figs. 6, 7, 8, Plate I.). The absence of granular ventricles, of perivascular infiltration with lymphocytes and glia cells and the existence of normal pyramidal cells arranged in columns mark a distinction from progressive paralytic dementia, with which this condition by a careless observer might be confused.

The healthy condition of the pyramidal layer of cells (*vide* Fig. 3, Plate I.), which is always affected markedly in general paralysis, accords with the statement by Dr. Stewart, that "he frequently conversed with the patient during the lucid intervals, and his conversation then was rational and well sustained." The mental condition was, therefore, mainly due to toxæmia, and not decay and destruction of the neural structures of the cortex.

The physiognomical expression of the individual, as shown in the photograph, exhibits "a wild appearance," a mild degree of terror and of

pain; it would accord very well with *delirium tremens*, which the notes indicate rather was his condition on admission. At the same time the notes distinctly state that he had not been drinking recently. Cases of pseudo-general paralysis have been described due to lead, and though more likely to occur in those who are intemperate yet it occurs in those who are temperate, and therefore must be due, directly or indirectly, to the lead poisoning. There is usually in such cases a sudden onset with violent delirium, motor restlessness, epileptiform seizures and hallucinations generally of a terrifying character, associated with loss of memory, mental confusion, and delusions of persecution, *e.g.*, of being followed or of being poisoned. These symptoms combined with muscular tremors and speech affection make up a clinical picture in some respects very like general paralysis; but the history of lead poisoning, the sudden onset, and the hallucinations of sight and hearing together with lucid intervals are unlike ordinary general paralysis and more like *delirium tremens*. There was apparently some evidence of lead accumulation observed in this case in the abdominal organs at the *post-mortem* examination; sections of the liver, however, were cut and placed in ammonium sulphide without any definite apparent change. The fact that although his wife was a widow and had had four healthy children by her first husband, "and although she was still in the child-bearing age" had no children by this man (although he was not impotent), is in support of the pernicious influence of the lead on his whole body; for there is a considerable amount of evidence to show that chronic lead poisoning affects the germ plasma in the male and produces sterility. In the female, it is well known and an accepted fact, that lead poisoning produces sterility, miscarriages and abortion; it is even taken by women in the form of emplastrum plumbi as an abortifacient.

Dr. Oliver, in his interesting article in Clifford Allbutt's system of medicine, states that only a few cases have ended fatally, and in these the *post-mortem* appearances were those of ordinary general paralysis; on chemical analysis, however, lead was found in the brain. In this case I have shown that the microscopic appearances were not like general paralysis neither were the macroscopic appearances. The brain weight was that of an average man; there was only slight excess of fluid and therefore there could have been but little wasting, and there were no granulations in the ventricles. It might be argued, therefore, that this was not a case of lead encephalitis. Von Jacksh (Die Vergiftungen Nothnagel's system), however, describes the case of a young female porcelain painter who died with all the signs and symptoms of severe brain affection, yet no trace of lead could be found in 529 grammes of brain substance. So that it is difficult to decide whether the case of

Dr. Stewart's above recorded should be regarded as one of chronic lead encephalitis or a chronic encephalitis indirectly due to the effect of lead by the changes this poison has worked in the body in causing an interstitial nephritis and arterio-sclerosis, which combined with chronic alcoholism caused a meningo-encephalitis. Von Jacksh points out that chronic lead poisoning interferes with the oxidation processes and leads to gout and interstitial nephritis.

#### DESCRIPTION OF PLATE I.

- Fig. 1.—Three cells from anterior horn of the spinal cord cervical enlargement, showing one large cell with very marked chromatolysis, the Nissl granules are almost absent; adjacent are two fairly normal smaller spinal motor cells. Magnification 400.
- Fig. 2.—Giant pyramidal cell from motor area with marked chromatolysis and eccentric nucleus. Magnification 400.
- Fig. 3.—Two large pyramidal (association) cells, showing normal Nissl granules and processes. Magnification 350.
- Fig. 4.—Giant pyramid from the face area of the motor cortex, showing less advanced change of the cytoplasm; there is a perinuclear chromatolysis, and the nucleus is eccentric. Magnification 400.
- Fig. 5.—Small cells of Vagus nucleus of the medulla, showing various stages and degrees of perinuclear chromatolysis. Magnification 400.
- Fig. 6.—Cortex stained by Cajal silver method, showing a large mesoglia cell sending processes on to the wall of a small vessel. These neuroglia cells were extraordinarily numerous throughout the grey matter of the cortex and in the subjacent white matter. Magnification 430.
- Fig. 7.—Small hyaline degenerated arteriole in the pia-arachnoid of the spinal cord. This shows the usual appearance met with in the small vessels, and is typical of arterio-sclerosis (arterio-capillary fibrosis). Magnification 750.
- Fig. 8.—Section of the base of a pyramid of the renal cortex; it shows marked interstitial fibrosis; a number of the tubules are devoid of epithelium and contain casts—stained deep purple by the hæmatoxylin. Magnification 250.
- Fig. 9.—Section of cerebral cortex of a worker in lead who died of progressive paralytic dementia (G.P.I.). The perivascular infiltration with lymphocytes and plasma cells is shown. Magnification 200.

PLATE I.

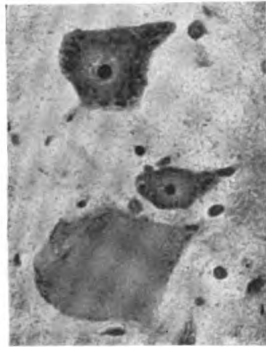


FIG. 1.  
Cervical Cord. Mag. 400.

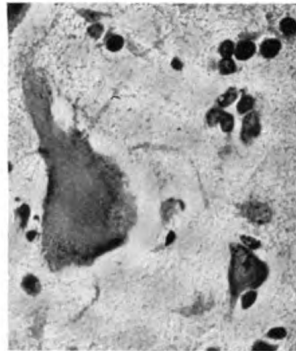


FIG. 2.  
Cortex. Mag. 400.



FIG. 3.  
Cortex. Mag. 350.

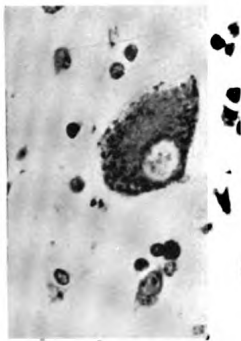


FIG. 4.  
Cortex. Mag. 400.

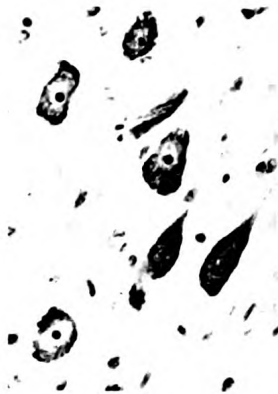


FIG. 5.  
Vagus Nucleus. Mag. 400.

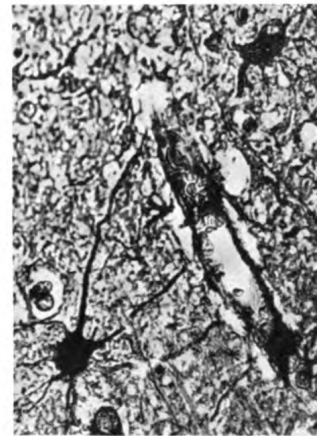


FIG. 6.  
Mag. 430.

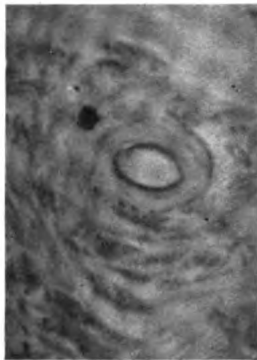


FIG. 7.  
Mag. 750.

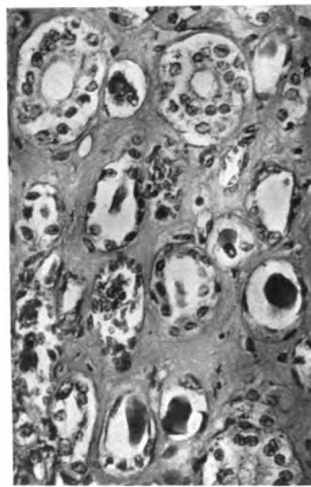


FIG. 8.  
Mag. 250.

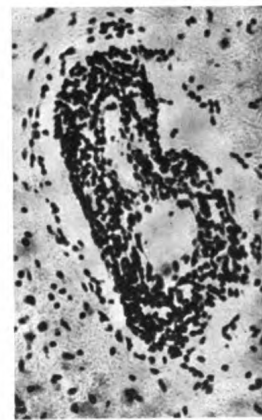


FIG. 9.  
Cerebral Vessel. G.P.I.  
Mag. 200.



## A CASE OF EMBOLISM OF THE ANTERIOR DIVISION OF THE LEFT MIDDLE CEREBRAL ARTERY.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

The notes of this case are very deficient; I only once saw the patient myself. For this reason the brain was not kept for microscopic investigation, but there are some points of interest worthy of record.

### CASE BOOK NOTES.

A. G., æt. 49. Admitted to Claybury Asylum, transferred from Fisherton House, 1/11/94.

*History previous to admission.*—Married. Occupation, artificial flower maker. Alcoholic excess.

*Medical certificate.*—Noisy, raving and violent. Tears at those around her. Refuses food. Seems to be under the delusion that her daughter is being murdered. Restless and constantly dressing and undressing herself.

*Condition on admission.*—*Physical:* Has marked right facial paralysis, lips and face drawn over to the left side. Marked motor aphasia. Articulation very thick and indistinct. Deep reflexes exaggerated on right side. Inco-ordination of right arm and leg. Heart hypertrophied. Lungs impaired resonance and coarse rales at the left apex. Pupils irregular, react to light and accommodation.

*Mental.*—Quiet and obedient, depressed at times, very incoherent, speech bad, cannot be understood. Melancholic in appearance. Clean in her habits. Eats and sleeps well.

21/12/94: Mania, with general paralysis. Incoherent, unable to answer questions.

21/12/96: Secondary dementia. Excited and noisy at times. Aphasia, and her memory is impaired, also her articulation, and it is difficult to understand what she says.

22/5/98: Restless, noisy, dances wildly about the airing court, and as her right leg is somewhat spastic her movements are more or less in a circle, from left to right. At times very spiteful and bad tempered.

20/12/99: Recurrent mania. Memory much impaired. No idea of time or place. Restless, noisy and abusive.

2/12/02: Getting worse mentally, being more lost, dirty and demented. More feeble and cannot walk well.

30/6/03: Is in bed in D.I. in a very feeble state, and in the last stage of general paralysis. Pupils 2 mm., contour regular. K. J.'s exaggerated. Muscular movements very inco-ordinate. Speech inarticulate. Breathing bronchial with moist rales over both lungs, most marked at left apex. There is much detraction at both apices.

4/7/03: Died this evening at 6.28 p.m.

In October, 1897, my attention was called to the case, and I took the following notes:—

She is suffering from facial paralysis, very marked of the right lower half of the face with tongue deviating to the right; there is some right hemiparesis. Knee jerks very exaggerated, patellar and ankle clonus of right leg. Marked wrist tap and triceps jerk on right side. She has a fairly good grasp with the right hand, *but she is unable to write or use a needle*, which she could do before she had the apoplectic attack. She can pick up a needle with the right thumb and forefinger and she helps in various ways in the wards. She carried a cup filled with water to her lips by placing the cup on the palm of the right hand and then grasping with the thumb and fingers. She could not take it with safety by the handle.

She can close both eyes, but neither one independently, although she tried to do so. *She understands everything that is said to her, and quite understands everything that is written down.* The following questions were asked her in writing or orally. She indicated by an affirmative or negative sign of the head, as she was quite unable to express her thoughts in comprehensible spoken language; the words were usually either misplaced, inappropriate, or incomprehensible owing to her difficulty of utterance. Sentences in which the words had any logical sequence were not uttered. She understands what is said to her for she obeys commands.

The following sentences were written down:—

Did you lose consciousness when you were paralysed?—To this question she made signs and gestures that she was asleep when she lost her speech.

Had she a fit?—Negative sign.

Had you any headache?—Negative sign.

Were you in good health?—Affirmative sign.

Could you walk the next day after you lost your speech?—Affirmative.

Could you use your hand?—Partial affirmative, pointing to her hand as if weakened.

Your age is 54?—Affirmative.

Are you married?—Affirmative.

Have you a son?—Affirmative.

Have you a daughter?—Affirmative.

When making these signs she would try to speak, but I could not understand what she said.

How long have you lost your speech, 4 or 5 years?—This was written down and she pointed to 5.



Pupils equal, react to light and accommodation. Some hemiparesis of leg and arm, but gait is not hemiplegic; the leg is somewhat spastic. She occasionally has attacks of excitement which are, I am informed, followed by depression. It seemed to me that this was partially due to the fact that she could understand, but could not make others understand her wants; for she indicated to me by signs and occasionally words that she wished to go away from these people.

*Diagnosis.*—Softening with destruction of Broca's convolution and of the face and arm centres of the left hemisphere.

Abstract of *post-mortem* notes:—

Emaciated. Poor physique. Muscles pale and wasted.

Abdomen distended and becoming greenish-purple in colour.

Nebula on front of right cornea.

Considerable excess of fluid in sub-dural and sub-arachnoid spaces.

The greater part of the central convolutions of the left hemisphere are markedly wasted and softened. The whole brain was removed and placed in Müller's fluid for further examination. *Weight* 1,210 grammes.

Fourth ventricle only very faintly granular.

Pons, medulla and cerebellum: *Weight* 175 grammes.

Neck: Small movable tumor of skin in region of thyroid cartilage.

*Thorax.*—Right pleura, apical adhesions. Left pleura, generalised adhesions.

Bronchi: Congested and œdematous. Bronchial glands: Enlarged, but not caseous.

Right lung: 680 grammes, apex nodular. No caseation or cavitation. Whole lung œdematous and congested.

Left lung: 590 grammes: old adherent pleurisy, with formation of calcareous plate over posterior border; the organ was carnified.

Heart: Muscle substance soft and flabby.

Valves: Old endocarditis of mitral valve.

Coronary arteries: Orifices atheromatous.

Aorta: Atheromatous especially in descending part.

*Abdomen.*—Liver: Fatty, fibroid and covered with lymph.

Kidneys: Fatty, cortex diminished, capsule strips leaving granular surface.

Generalised peritonitis and acute intestinal obstruction from volvulus of large intestine.

*Cause of death:*—

1. Acute intestinal obstruction from volvulus with generalised peritonitis.

2. Endocarditis, mitral valve.

3. Old embolism of anterior division of left middle cerebral. Softening of the left hemisphere corresponding to its area of distribution.

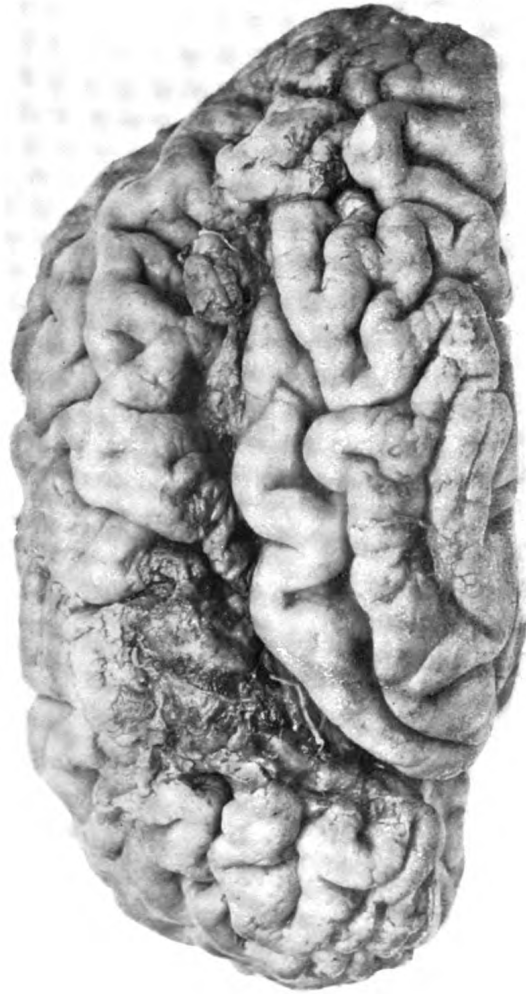
*Brain.*—On removing the membranes the following appearances were noticed:—As a result of embolism of the left middle cerebral artery probably only the anterior branch (as judged from the area of softening) was blocked. The temporal lobe presents no appearance of softening or atrophy, the lesion being limited below by the sylvian fissure. The superior frontal and the anterior half of the second frontal present no atrophic change; it may be remarked that the second frontal is reduplicated, consisting of two convolutions, which connected at their anterior end are joined with the first frontal. The posterior half of the lower division of the second frontal presents an atrophied appearance with little depressions on its surface indicating thickening of the membranes. The third frontal, or rather what remains of it, is atrophied similarly to the second frontal. The part of it corresponding to Broca's convolution, namely, the *pars basilaris*, with its connection to the ascending frontal has completely disappeared. The atrophy also involves the *pars triangularis* and extends to the *pars orbitalis*; this extension of the atrophy to the orbital surface becomes apparent on comparison with the right hemisphere.

Central convolutions: The whole of the lower two-thirds of the ascending frontal and ascending parietal convolutions are involved in the lesion, the upper part corresponding to the leg area is not involved owing to its supply by the anterior cerebral; thus the portions of the central convolutions which are connected in front to the superior frontal convolution and posteriorly to the superior parietal lobule are unaffected.

The lower third of the inferior parietal lobule, including the marginal, is atrophied, and on section it is seen that the Island of Reil is atrophied in its whole extent, as well as the upper portions of the *gyri transversales* which connect the temporal and parietal lobes. As the photograph of the left hemisphere shows, the first temporal convolution, including its posterior third, is entirely free from atrophy. There is a little atrophy, as shown by a worm-eaten appearance, in the second and third temporal convolutions of the left hemisphere, but not like that due to embolic softening. It is probably the result of secondary atrophy of functionally correlated structures. Examination of the right hemisphere shows the following remarkable changes: A secondary symmetrical atrophy of the second and third frontal convolutions, whereas the superior frontal shows but little change. The posterior half of the second frontal and the greater part of the third frontal exhibit a shrivelled and worm-eaten appearance like that which appears in various regions described on the left side. There appears also to be a slight secondary atrophy of the lower two-thirds of the central convolutions, but this is not so apparent. Elsewhere the right hemisphere presents no structural defects. These



PLATE I.



Photograph of left hemisphere showing lesion.

changes are in all probability due to atrophy of association fibres which connect similar functionally correlated regions of the two hemispheres.

*Spinal cord.*—There was well-marked naked-eye degenerative sclerosis of the direct tract which could be traced down the left side of the spinal cord as far as the eighth dorsal. There was well-marked diffuse degenerative sclerosis in the right-crossed pyramidal tract which was less evident.

*Remarks.*—It is certain that this patient did speak, although it was for the most part incomprehensible jargon, still there was not a complete motor aphasia. When I saw her I came to the conclusion that we should find the lesion that was discovered *post mortem*. The secondary atrophy in the same convolutions of the opposite hemisphere and in associated structures concerned with the function of speech of the same hemisphere is of interest. Also the fact that the second and third temporal convolutions of the left hemisphere should show a more marked secondary atrophy than is seen in the first temporal, would suggest some functional association of this portion of the cortex with the region of the brain most atrophied, viz., the lower two-thirds of the central convolutions.

## A BACTERIOLOGICAL INVESTIGATION OF GENERAL PARALYSIS.\*

By J. P. CANDLER, M.A., M.D. (CANTAB), D.P.H., Assistant Pathologist to the  
London County Asylums.

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\* Accepted as a thesis for the degree of M.D. of Cambridge University.

## INTRODUCTION.

The purpose of this thesis is to describe the result of a research in which I have been engaged for nearly a year in the Pathological Laboratory of the London County Asylums, and to record the conclusions at which I have arrived as the result thereof.

The line of study was suggested to me by Dr. F. W. Mott, the Director of the Laboratory, as one suitable for investigation, and also because of the theory which has recently been brought forward that general paralysis of the insane is a bacterial toxæmia dependent upon the action of a certain group or groups of diphtheroid organisms.

My investigations, which have been mainly directed to the detection and isolation of diphtheroid organisms from cases of general paralysis, and as a control, from other forms of insanity, have comprised:—

- (1) The examination of the blood, cerebrospinal fluid, respiratory, alimentary and genito-urinary tracts of the cadaver.
- (2) The examination of the urine and urethras during life.
- (3) The examination of the circulating blood, and the cerebrospinal fluid withdrawn by lumbar puncture, during life.

For the sake of clearness I propose to record the result of my investigations in the order I have mentioned, but first I would briefly state the main objects I had in view at the commencement and throughout the whole of the work. The special organisms which I wished to detect and isolate were to be those which could be grouped under the class of *diphtheria-like bacilli*, with the exception of the bacillus of Hofmann, which has not been suggested as an etiological factor in the production of general paralysis.

## DESCRIPTION OF METHODS EMPLOYED.

The media employed during the course of the research were: bouillon, agar-agar, serum agar, blood serum, gelatine, peptone water, potato, and solutions of the sugars in 1% peptone water. In the earlier part of the investigation byno-hæmoglobin agar, made from Allen and Hanbury's byno-hæmoglobin, was prepared and used according to the instructions of Dr. Ford Robertson, who claimed that this medium caused the metachromatic granules or polar bodies, so frequently seen in stained films of diphtheria-like organisms, to stand out with special clearness. In a few instances I was able to confirm this observation, but I found that the medium in most instances tended to produce atypical forms, while the cultures quickly died out; latterly, therefore, I decided to abandon it.

For staining reactions, Loeffler's methylene blue, carbolic methylene blue, Gram's stain and Neisser's method for the differentiation of polar bodies were used; the latter stain, however, showed no advantages over well-prepared specimens stained by either of the methylene blue preparations.

For the separation of diphtheroid bacilli from colonies of other micro-organisms which might be present, I used, in nearly every case, Petri dishes containing a thin layer of solidified blood serum, serum agar or agar-agar. After preparation, these plates were placed in the incubator at 37° C. for 24 hours to ensure that they were sterile. They were used as follows: One or more loopfuls of the suspension to be plated were deposited on the medium in the Petri dish and smeared over the surface by means of a sterile L-shaped glass rod; a second and third plate were similarly smeared with the glass rod without further addition of the suspension. In this way it was possible to obtain a plate which contained a fair number of colonies, sufficiently discrete to allow of their isolation and examination. This method is in common use for diluting suspensions of intestinal bacteria over the surface of plates containing special solid media such as MacConkey's bile salt agar, or the Conradi-Drigalski medium, and possesses the advantage over other methods of plate cultivation that any colonies which appear are situated on the surface of the medium and can be dealt with readily.

#### THE EXAMINATION OF POST-MORTEM MATERIAL.

The blood, cerebrospinal fluid, respiratory, alimentary and urinary tracts of 84 cases were examined. Twenty-five of these were general paralytics and the remaining 59 comprised other forms of insanity.

The method of collecting the material was as follows:—

The heart was raised so as to expose the inferior vena cava; the wall of this vessel was seared with a cautery; the sharp end of a sterile glass pipette thrust into the lumen and five to ten cubic centimetres of blood were removed from the vein and distributed into two or three tubes of sterile bouillon which were placed in the 37° C. incubator for further observation. The cerebrospinal fluid was obtained by thrusting a sterile glass pipette into the lateral ventricle through the corpus callosum, while the brain was still *in situ*. The spot for puncture was exposed by gently separating the cerebral hemispheres so as to display the corpus callosum freely, the searing iron being applied to a small part of the surface previous to the introduction of the pipette. Part of the cerebrospinal fluid was pipetted into a sterile centrifugal tube and the centrifuged deposit smeared over the surface of sterile agar or serum agar



plates, while a second sample was placed in a sterile culture tube without the addition of any culture media.

The material from the lungs was obtained by inserting a stout looped platinum wire down one of the smaller bronchi. A tube of bouillon and a series of slanted blood serum and agar tubes were inoculated. Scrapings from the mucous membrane of the stomach and intestine were treated in a similar manner. The serous surface was seared with the cautery and the incisions into these organs were made with sterile instruments. The urine was collected from the bladder by means of a sterile pipette, which was thrust through the wall of the organ after the surface had been thoroughly seared; the centrifuged deposit of about 10 c.c. was at once plated, while, as a control, about 1 to 2 c.c. of the urine were pipetted into a broth tube. All the cultures obtained were placed at once in the 37° C. incubator and examined at the end of 12 to 24 hours for the presence of diphtheroid bacilli. In successful cases these were isolated and sown in pure culture over the surface of blood serum tubes and their morphological characters and cultural reactions on other media recorded.

The 25 cases of general paralysis so examined yielded diphtheroid organisms in three, or 12%.

In Case I. a diphtheroid organism was obtained in pure culture from the blood, and from the respiratory tract in association with other organisms. A film preparation from the cerebrospinal fluid, after incubation, showed the presence of a bacillus similar to that obtained from the respiratory tract in very scant numbers among a host of other organisms; attempts to isolate it were not successful. The organism obtained from the blood was very typical and differed in many respects from that isolated from the respiratory tract, which appeared to belong to a different species. The principal characters of the former, after cultivation on blood serum for 24 hours were as follows:—A non-motile, non-sporing, Gram-positive organism. Stained with Loeffler's methylene blue, the bacilli were of medium length, very slender and straight or slightly curved.

At this stage of growth they presented the characters of tapering bacilli, each of which appeared to possess a definite unstained transverse septum, causing the organism to look like two bacilli of triangular shape with their bases in apposition. The ends of the bacilli tapered to an extremely fine point, and, in many instances, stained very faintly (the so-called sheath form). Metachromatic granules were present in abundance. The characteristic grouping of the diphtheria bacilli was well seen in stained preparations (Fig. I.).

After two to three months' incubation at 20° C. the bacilli had lost

some of their original characters, there being a tendency on the part of some to stain very faintly, while some slender thread forms were also found. The number of bacilli with metachromatic granules was far less than in the original culture and the Neisser reaction was very faintly marked.

*Cultivation.*—On agar and blood serum plates the colonies appeared as small circular dots at the end of 48 to 72 hours, rather opaque, white in colour, the centre somewhat raised and denser than the periphery, of which the margin was quite regular (Fig. XIV.). In size they varied from 2 to 4 mm. in diameter.

In bouillon the growth was attended by an initial turbidity, followed by the deposition of a finely granular deposit on the sides of the test tube.

On potato the growth was invisible to the naked eye.

In litmus milk media the growth was not attended by any apparent change.

A well-marked acid reaction occurred in glucose peptone water, but the organism had no effect on lactose.

No liquefaction of gelatine occurred after six weeks' incubation at 20° C.

The inoculation of bacillary emulsion into a guinea-pig produced no result.

From the same case the respiratory system, including both the trachea and bronchus, yielded a diphtheroid organism, which differed in several characteristics from that isolated from the blood in pure culture. In stained preparations the bacilli were almost completely of the segmented variety and somewhat longer and thicker. Here and there in the methylene blue preparation a few granules could be seen, but they were not displayed by the Neisser stain; the ends of some of these bacilli were decidedly pear-shaped or bulbous.

The growth on all solid media was far more luxuriant and moist than in the case of the true diphtheria bacillus, and the individual colonies were of larger size.

In bouillon the growth was attended by a decided turbidity without any deposit on the sides of the tube.

A visible dirty grey coloration attended the growth on potato.

The growth in milk gave rise to slight acidity but no coagulation.

There was no liquefaction of gelatine.

Growth in glucose peptone water gave marked acid reaction; the lactose peptone water remained unchanged.

The organism was non-motile, non-sporing and Gram-positive. It was also non-pathogenic to guinea-pigs.

In Case II, a diphtheroid organism was isolated from the respiratory tract of a general paralytic which agreed morphologically and culturally with that obtained from the respiratory tract of Case I.

In Case III, an organism of the diphtheroid species was isolated from the base of one of several circular erosions of the stomach of a general paralytic.

The growth on all solid media was very luxuriant and moist with large individual colonies.

On potato the growth was dirty grey in colour, moist and luxuriant.

The reaction in glucose peptone water was acid but in lactose peptone water no visible change occurred.

In bouillon there was a general turbidity, and after two days a somewhat stringy deposit had settled at the bottom of the test tube.

The growth in milk showed no visible alteration and there was no liquefaction of gelatine.

Stained specimens of a 24 hours' growth on blood serum showed the presence of bacilli of medium length but stouter than the true diphtheria bacillus. Polar bodies were present in almost every bacillus, but they were only very faintly stained by the Neisser method. The organism was non-motile, non-sporing and Gram-positive (Fig. VII.).

Fifty-nine cases of insanity other than general paralysis were examined *post mortem* in a similar manner.

Diphtheroid organisms were isolated in four cases or 6.6%. In three of the cases they were isolated from the respiratory tract and in the fourth case from a scraping of the urethral mucous membrane. The type obtained from this region was similar to that obtained from the urethras of cases examined during life and to which I shall shortly refer.

Of the three cases obtained from the respiratory tract, one agreed in all characteristics with those obtained from the respiratory system of general paralytics. The other two were similar to the diphtheria bacillus in staining reactions and cultural characters, but were of an extremely short variety. They were not pathogenic to guinea-pigs.

#### OBSERVATIONS ON THE STUDY OF POST-MORTEM MATERIAL.

The study of *post-mortem* material for the presence of diphtheroid organisms presents many difficulties. Firstly, the blood and cerebro-spinal fluid become invaded with organisms of all varieties immediately or shortly after death, and even with the aid of a cold chamber for the reception of bodies previous to autopsy it was rarely that I found these two fluids sterile, although I exercised every precaution to prevent external contamination. Secondly, the respiratory and alimentary systems contained such a wealth of organisms that the isolation of the

diphtheroid species involved a considerable amount of labour, and it is possible that in some cases they may have been outgrown or overlooked amongst the other forms which were present. Therefore I do not consider that observations attended with these difficulties should be looked on as of accurate statistical value; at the same time, however, my own observations do not lead me to think that diphtheroid bacilli are present in the cadaver with a sufficient degree of frequency to justify any claim to their importance.

#### EXAMINATION OF THE URINE AND URETHRAS OF LIVING PERSONS.

My attention was next directed to the examination of the genito-urinary tract of living individuals by reason of the statement of Dr. Ford Robertson that diphtheroid bacilli could be found in the urine of cases of general paralysis and locomotor ataxia with very considerable frequency. The method which I used for the examination was as follows:—

The urine was collected into sterile vessels after careful cleansing of the *meatus urinarius* and withdrawal by means of a sterile catheter. Part of the centrifuged deposit of about 10 cc. of urine was at once plated, while a second portion was placed into a tube of sterile bouillon.

Cultures from the urethra were obtained by inserting a small platinum loop as far as possible into the urethra after careful cleansing of the meatus. The loop was rotated several times in the canal and then smeared over the surface of two or more tubes of slanted blood serum and agar-agar. All the cultures so made were examined after 12 to 24 hours' incubation at 37° C.

#### EXAMINATION OF THE URINE OF GENERAL PARALYTICS.

Twenty-six cases of general paralysis yielded a diphtheroid bacillus in two cases, or 7.6%.

The two examples of diphtheroids obtained possessed identically similar characters. They were non-motile, non-sporing, Gram-positive organisms. On blood serum at the end of 24 hours the bacilli were of short to medium length, straight or slightly curved and grouped in small clusters. The granular type of bacillus was by far the most constant, but segmented forms were occasionally present. After 24 hours' growth on blood serum, pear-shaped and bulbous forms were frequently to be seen (Fig. V.).

On agar plates the colonies were slow to make their appearance and then became visible as small, extremely delicate, pearly white, circular colonies with even margins, somewhat similar to the growth of a streptococcus, with some tendency to adhere to the surface of the medium (Fig. XV.). The increase in size of the colonies was slow, but after five

or six days they became more spread out with margins slightly irregular and the centre raised and umbilicated.

In bouillon the growth was accompanied by a very fine granular precipitate, the supernatant fluid remaining clear.

Milk remained unchanged.

There was slight acid reaction in glucose peptone water, but none in lactose.

The growth on potato was invisible.

There was no liquefaction of gelatine and the growth on this medium was extremely scant.

Inoculation of guinea-pigs produced no effect.

#### EXAMINATION OF THE URETHRAS OF GENERAL PARALYTICS.

Thirty-one cases of general paralysis yielded diphtheroid organisms in 5 or 16%.

The first diphtheroid isolated was identical with those obtained from the urine.

The rest differed in only one particular, viz., that the colonies on agar plates were visible to the naked eye at an earlier date, and at the end of 76 hours showed a small but definite central umbilication, the growth from this to the periphery being flat and the margins slightly irregular. The colonies were somewhat flaky and did not tend to adhere closely to the surface of the medium (Fig. XVI.).

In bouillon the growth was attended by the formation of a very delicate scum or pellicle, a similar appearance being noted over the water of condensation at the bottom of the slanted agar tube. Microscopically there was no difference between this variety and that obtained from the urine.

#### EXAMINATION OF THE URINE OF CASES OF INSANITY OTHER THAN GENERAL PARALYSIS.

The urine of 28 cases of insanity other than general paralysis yielded a diphtheroid bacillus in one case, or 3·5%. It agreed in morphology and culture with those isolated from the urine of general paralytics.

#### EXAMINATION OF THE URETHRAS OF CASES OF INSANITY OTHER THAN GENERAL PARALYSIS.

From 44 cases of insanity other than general paralysis diphtheroid bacilli were isolated in 6, or 13·6%. All the types were similar to those already described (Figs. VI. and XVII.).

## OBSERVATIONS ON THE ABOVE EXAMINATIONS.

The examination of the genito-urinary tract of cases of general paralysis and other forms of insanity has revealed the presence of diphtheroid organisms which have differed in certain characteristics from those met with in other parts of the human body as ascertained from *post-mortem* investigation. Although not absolutely identical with the bacillus xerosis, they are, in my opinion, very closely allied to members of that group.

It is rather difficult to decide with certainty as to what part of the genito-urinary system affords a nidus for these organisms. In my opinion the examination of the urine, whether withdrawn by catheter or after it has been voided in the usual way, will fail to decide whether the organisms have come from the urethra or from the bladder, as by either method contamination with urethral organisms appears to be unavoidable. I am inclined to think that they exist mainly in the urethra, as I have not been able to obtain a growth of diphtheroid organisms from the urine which has been withdrawn at autopsy by puncture of the fundus of the bladder.

## EXAMINATION OF THE CIRCULATING BLOOD AND CEREBROSPINAL FLUID WITHDRAWN BY LUMBAR PUNCTURE.

*Technique.*—Blood in amounts varying from 5 to 20 cc. was removed from the basilic vein into a sterilised syringe containing a small amount of potassium citrate solution. The greater part of the blood was at once squirted into a flask containing about 100 cc. of sterile bouillon. As a control 0.5 to 2 cc. of the remaining blood was placed in a culture tube containing 10 cc. of broth. In addition the surface of a slanted agar and blood serum tube was also smeared over with drops of blood. In several cases anærobic methods of cultivation were used in addition to the ordinary procedure. The cultures were in the majority of cases transferred at once to the 37° C. incubator, but in a few instances they were placed for 12 to 24 hours in the ice chamber prior to incubation, as Dr. Ford Robertson has suggested, in order to diminish the possibility of phagocytic or lysogenic action of the blood, which, he asserts, destroys the diphtheroid organisms before they have an opportunity of multiplying in the culture medium. Previous to the withdrawal of the blood the skin of the arm was carefully cleansed to avoid as far as possible contamination from this source.

I have examined the blood of 27 cases of general paralysis on 45 different occasions during life, some cases having been utilised more than once. In no single instance have I been successful in obtaining a

culture of a diphtheroid bacillus. The majority of the cases selected were advanced cases of general paralysis, nearly all of whom have since died, and the clinical diagnosis has been verified at autopsy. In five of the cases the blood was obtained during the progress of, or shortly after, the termination of epileptiform seizures.

In 12 of the cases special efforts were made to obtain a culture of a diphtheroid bacillus from the bouillon flask inoculated with the blood of a general paralytic. After incubation at 37° C. for two to three days 20 to 30 c.c. were pipetted into two or more sterile centrifugal tubes, and the deposit thus obtained was smeared over the surface of sterile agar plates, or, as an alternative, was distributed into tubes of liquefied agar, and plates poured in the usual way. This method was adopted because by its use Dr. Robertson, of the Morningside Asylum, claims to have isolated a diphtheroid organism of the xerosis type from the circulating blood of several cases of general paralysis. My attempts to obtain a growth of a diphtheroid organism by this technique were unsuccessful. Nor have I ever seen, in stained films of the circulating blood or in films prepared from the centrifuged deposit of a bouillon flask after incubation, any organisms which I could accept as resembling diphtheroid bacilli.

The presence of other organisms in the circulating blood of general paralytics:—

In seven instances during my examination of the circulating blood I have obtained growths occurring in the broth flasks and tubes which I have been unable to account for on the theory of external contamination, although this is extremely liable to occur from the skin and from the atmosphere (*vide* Fig. XVIII.).

In four instances the organism was a staphylococcus albus; in one the colon bacillus; in one a small diplo-bacillus with occasional long forms resembling the bacillus of Friedlander; in one case a small delicate streptococcus, which was later obtained in pure culture from the heart blood at autopsy (Figs. XI. and XII.). These were all obtained from rapidly progressing cases of general paralysis and were probably factors in the production of the fatal termination.

Examination of the cerebrospinal fluid withdrawn by lumbar puncture during life:—

The cerebrospinal fluid of nine cases of general paralysis and one of tabes dorsalis was examined. In the last seven cases the centrifuged deposit of 10 c.c. was plated directly in a manner similar to that used in the examination of the blood, and the rest of the fluid was placed in broth tubes and on the surface of slant agar tubes. I did not succeed

in obtaining a culture of a diphtheroid organism from this fluid, neither did I see any diphtheroid bacilli in stained films of the deposit.

#### ANALYSIS OF THE RESULT OF THE ABOVE INVESTIGATION.

*The examination of post-mortem material.*—Twenty-five cases of general paralysis yielded diphtheroids in three, or 12%. Fifty-nine cases of insanity other than general paralysis yielded diphtheroids in four, or 6.6%.

*Examination of the genito-urinary tract.*—Fifty-seven cases of general paralysis yielded diphtheroids in seven, or 12.3%. Seventy-two cases of insanity other than general paralysis yielded diphtheroids in seven, or 9.7%.

The total number of cases examined was 213, 82 of which were cases of general paralysis and 131 were of other forms of insanity.

The percentage incidence of diphtheroid organisms in general paralysis was 12.2, while in other forms of insanity it was 8.4.

I have not included in these figures the cases in which the blood and cerebrospinal fluid were examined during life, the results of which, as far as diphtheroid organisms are concerned, were entirely negative.

#### THE PRESENCE OF DIPHTHEROID ORGANISMS IN NATURE.

Evidence of the ubiquitous nature of the diphtheroid group of organisms has rapidly accumulated since the discovery of the Klebs-Loeffler bacillus. Organisms resembling the true diphtheria bacillus have been found in almost every part of the human body and also in domestic animals and birds, some virulent and others non-virulent to laboratory animals and to man. Graham Smith gives a very complete bibliography wherein they are stated to have been found in the normal eye, the mouth, nose, ear, the lesions of vaccinia and variola, the lesions of leprosy, eczema and other skin lesions, the female genital organs, the male urethra, the urine, the pus of a liver abscess, the valvular lesions of ulcerative endocarditis, milk, the lungs of rats, the eyes of normal guinea pigs and dogs, the mouths of diseased and normal birds, etc.

Hudson and Pantou in an investigation of 105 cases of acute conjunctivitis, found diphtheroid bacilli in no less than 60.

Stanziale obtained a diphtheria-like bacillus in 12 out of 27 cases from the normal urethral mucous membrane. He quotes the work of Pfeiffer, who in 15 examinations of normal urethras found diphtheria-like bacilli in 11.

Stuart McDonald found diphtheria-like bacilli in the cerebrospinal fluid of cerebrospinal meningitis on three occasions, during a series of



over 30 autopsies; in two instances in association with the meningococcus and once in pure culture.

Morrell and Wolf record a case of meningitis, from the cerebrospinal fluid of which, both by lumbar puncture during life and also after death, a diphtheroid organism was isolated.

At a meeting of the Medico-Psychological Association in May, 1907, the frequency of diphtheroid organisms in cases unassociated with insanity was commented upon by Dr. Eyre, of Guy's Hospital, and Dr. Dean, of the Lister Institute. Dr. Eyre stated that during the routine examination of from 500 to 600 specimens he had found diphtheroid organisms in the cerebrospinal fluid withdrawn during life, and from the plural exudate of a case of tuberculosis meningitis; also twice in cultivations of blood from cases of suspected infective endocarditis, once in a case of tuberculosis cystitis, and once from material obtained from a case of disease of the antrum. He also stated that those who had any experience in the examination of material obtained from general hospitals were aware that diphtheroid organisms were of extremely frequent occurrence.

Dr. Dean also commented upon the extraordinarily wide distribution of diphtheroid bacilli in nature; that they were frequently met with in disease, in accidental association with the organism responsible for that disease; also that they could be found in many normal conditions, *e.g.*, in the male and female smegma and other sebaceous secretions, in urine, and very commonly in milk, which might possibly account for their presence in the stomach of cases of general paralysis. He also stated that Dr. Arkwright, working at the Lister Institute, had found diphtheroid organisms in two out of seven cases of suspected cerebrospinal meningitis in which he examined the brain and meninges *post mortem*. Further, out of 23 cases in which he had examined cerebrospinal fluid he found diphtheroid organisms on two occasions. These were sometimes associated with other organisms such as the meningococcus.

In view of these facts he thought that great caution should be observed in accepting any diphtheroid organism as having a causal relation to general paralysis, unless it possessed well-marked characteristics, including pathogenic action on experimental animals.

The incidence of diphtheroid organisms in cases of general paralysis and other forms of insanity has formed the subject of an investigation by Eyre and Flashman, who found diphtheroid organisms present in 16.6% of general paralytics, as compared with 17.6% of other forms of insanity. Their conclusions were based on the examination of the throats of a large number of cases suffering from all forms of insanity and also of material obtained at *post-mortem* examinations. They stated

that in their hands diphtheroids could not be isolated from cases of general paralysis any more readily than from other forms of insanity.

Dr. George Robertson, of the Morningside Asylum, claims to have isolated a diphtheroid bacillus from the circulating blood or cerebro-spinal fluid of seven out of 14 cases of general paralysis; in three of these the organism is stated to have been seen in stained preparations of the fresh blood. He states that his organism is not identical with Ford Robertson's *Bacillus paralyticans*, which he has never isolated. He has also found the same bacillus in other forms of insanity in acute cases.

#### CONCLUSIONS.

The conclusions at which I have arrived as the result of my own investigations, together with those obtained by other observers, are:--

(1) That diphtheroid organisms, some pathogenic and others non-virulent to man and animals, are extremely common organisms in nature.

(2) That they can be found with considerable frequency and representing several different species in all parts of the human body, but especially on serous and mucous surfaces.

(3) That the genito-urinary tract affords a very frequent nidus for some varieties.

(4) That diphtheroid organisms may be found either in pure culture or associated with other micro-organisms in diseases which have been proved beyond doubt to be due to another specific factor.

(5) That my own observations lead me to believe that diphtheroid organisms cannot be isolated from cases of general paralysis with any greater ease or frequency than from cases unassociated with that disease.

(6) That during the progress of general paralysis the impairment of tissue resistance facilitates the occasional entry of micro-organisms into the blood stream.

(7) That the organisms which gain entry are not confined to any particular species, but may include several varieties among which, according to the observations of others, the diphtheroid class must be included.

#### THE BACILLUS PARALYTICANS OF FORD ROBERTSON.

In a series of articles which have appeared from time to time during the last few years Drs. Ford Robertson and McRae have claimed that an organism of the diphtheroid species is the specific etiological factor in general paralysis and tabes. The contention of these observers seems to be that, although such agents as syphilis, alcohol and excess of nitrogenous diet, individually or collectively, may serve as predisposing

factors by undermining the tissue resistance, yet without the *Bacillus paralyticus* there can be no general paralysis or tabes.

The grounds on which they have based their contention appear to be:

- (1) The discovery of diphtheroid organisms with great frequency in the alimentary, respiratory, and genito-urinary system of all cases of advancing general paralysis.
- (2) The experimental production of general paralysis in rats.
- (3) The success which they claim to have attended the treatment of certain cases of general paralysis and tabes dorsalis by vaccines and antisera prepared from their organisms.

I will therefore draw attention to some of the statements they have made in support of their claims, and will attempt to criticise such of them that appear to require further substantiation.

Firstly, with respect to the frequency of diphtheroid organisms in cases of general paralysis, Ford Robertson and McRae state: "The evidence that a diphtheroid bacillus—either an attenuated form of the Klebs-Löffler bacillus or more probably an altogether distinct micro-organism—is the specific etiological factor in general paralysis and tabes dorsalis is briefly as follows: A bacillus of this nature is, according to the results of our investigations, present in large numbers, either in the alimentary or respiratory tract, or in both, and in the genito-urinary tract, in all cases of advancing general paralysis. This bacillus has a thread form, which has been found invading the walls of the respiratory or alimentary tract in five cases of general paralysis. It can be shown that this bacillus invades the pulmonary tissues in cases of general paralysis, and it is commonly the only micro-organism present in large numbers in the catarrhal pneumonic foci that occur in most of such cases dying in congestive attacks. A growth of a diphtheroid bacillus has now been obtained in cultures made from the brain *post mortem* in ten cases of general paralysis out of 24 in which cultures were made from this organ. Diphtheroid bacilli exhibiting metachromatic granules in Neisser preparations have been detected in the fresh blood in one case and in sections of the brain in two cases. It has been ascertained by experimental methods that these diphtheroid bacilli in contact with the living blood are rapidly taken up by the polymorpho-nuclear leucocytes, and that they may be completely digested in the course of two or three hours. Bodies exactly corresponding in appearance to these dissolving bacilli can be detected in the blood and the cerebrospinal fluid of the living general paralytic, especially during a congestive attack. Whilst the fact that most of the bacilli present are in process of disintegration satisfactorily explains the long succession of negative results of

endeavours to obtain cultures from the blood and cerebrospinal fluid, we have, by the use of special methods, succeeded in obtaining pure growths of a diphtheroid bacillus from the fresh blood in four cases of general paralysis, and from the cerebrospinal fluid withdrawn by lumbar puncture in two cases. In sections of the brain prepared by special methods disintegrating diphtheroid bacilli can be recognised in the walls of the vessels and in the pia-arachnoid in many cases of general paralysis. The centrifuge deposit from the urine of the general paralytic, especially during a congestive seizure, commonly contains abundant diphtheroid bacilli that have been more or less affected by lysogenic action. In seven consecutive cases of general paralysis, combined with tabes, we have found the centrifuge deposit from the urine to contain, not only these altered diphtheroid bacilli, but also living ones, showing distinct metachromatic granules. In such cases a culture of the bacillus can be obtained from the urine."

Further observations have led them to suppose that there are at least two types of diphtheroid bacilli capable of producing general paralysis and tabes dorsalis. These they have named *Bacillus paralyticans longus* and *Bacillus paralyticans brevis* respectively, the latter bearing a close resemblance to the bacillus xerosis and being found most frequently in the urine. Furthermore they have suggested that the frequency with which diphtheroid organisms can be found in cases free from mental disorder has no particular bearing upon the point at issue; but, if their organism is to be classified as specific, it must be shown to possess special distinctive characters. These the *Bacillus paralyticans* has not yet been shown to possess so far as morphology and cultural characters are concerned, and until its specific pathogenic property has been conclusively demonstrated, I maintain that the presence of organisms of a similar species in cases unaffected with general paralysis cannot be considered to be of secondary importance.

The great difficulty which these observers have experienced in cultivating the diphtheroid organisms from the circulating blood and cerebrospinal fluid is worthy of consideration. This apparently cannot be due to paucity of numbers, for bacilli possessing metachromatic granules are stated to have been seen in stained films made from a drop of the circulating blood. They must therefore be present on occasions in the blood stream in enormous numbers to allow of their identification in a blood film and should certainly be capable of cultivation if two or three cubic centimetres be placed into a suitable culture medium and incubated at body temperature.

The reason assigned by Ford Robertson for this failure is that the bacilli are rendered inert, partly by the phagocytic properties of the

leucocytes, and partly by the lysogenic action of the blood serum, and other fluids. As evidence of this he states that in stained films of the blood, cerebrospinal fluid and urine, and in sections of the brain, bodies corresponding to dissolving diphtheroid bacilli are almost constantly present. I have examined a considerable number of stained films of the blood, cerebrospinal fluid, and sections of the brain, and have never been able to detect diphtheroid bacilli. With regard to the *débris* seen in films of the cerebrospinal fluid and in sections of the brain I think it would be very difficult to form any precise opinion as to its nature, and more difficult still to recognise disintegrating bacilli.

This lysogenic action of the serum has been disputed by Dr. Bulloch, Bacteriologist to the London Hospital, who states: "If diphtheroid bacilli exist in the blood or cerebrospinal fluid of general paralysis they should be capable of cultivation at once without waiting for the cessation of any supposed bactericidal action, for no lysogenic action of the serum for bacilli of this group has been proved to exist."

My own experiments performed *in vitro* do not support the observations of Ford Robertson. I have subjected two strains of diphtheroid bacilli obtained from cases of general paralysis to prolonged contact with the serum of patients suffering from that disease. Emulsions from a 24 hours' agar culture of the organisms have been mixed with fresh serum from a general paralytic in known proportions, and placed in sealed tubes in the 37° C. incubator for 24 hours. Control experiments with normal serum were made. The contents of the tubes were then blown out into melted agar and plates poured in the usual way. The results obtained, as estimated by the number of colonies growing up on the plate cultures, showed practically no difference in inhibitory power between the two types of serum employed. Further, stained films made from the diphtheroid bacilli which had been exposed to the action of undiluted serum of general paralytics for 24 hours at 37° C. showed little if any alteration in the shape and staining reactions of the bacilli. (Compare Figs. I., II., III., IV.)

#### THE PRESENCE OF BACTERIA IN FILMS OF THE BRAIN AND MENINGES.

Dr. Ford Robertson states that he has found diphtheroid bacilli with metachromatic granules present in sections of the brain of general paralytics on two occasions. I have been unable to confirm these observations. On the other hand I have found bacteria of various kinds present in the stained films of the brain and meninges, and I show three photomicrographs to illustrate this point. Fig. VIII. shows micro-organisms in a smear preparation of the cortex of a female general paralytic. This

patient died from the exhaustion of very severe and numerous epileptiform seizures. The autopsy was performed one hour after death. The blood and cerebrospinal fluid both contained several varieties of micro-organisms on cultivation, but diphtheroid bacilli were not found. Fig. IX. shows micro-organisms in a smear preparation from the cortex of a male general paralytic made 22 hours after death, the body in the meantime having rested in the cold chamber. Fig. X. shows a strepto-bacillus in another field of the same preparation. I produce it to emphasise how deceptive microscopic evidence might be. This strepto-bacillus possesses several very well defined and deeply stained granules. Had this organism been broken up into two or three portions during the preparation of the film the separate parts would have borne a remarkable resemblance to diphtheroid bacilli with metachromatic granules. These three photomicrographs, especially the first, serve to substantiate what I have previously said concerning the almost invariable presence of micro-organisms in the blood and cerebrospinal fluid obtained *post mortem*, and offers presumptive evidence of microbial invasion of the tissues in the terminal stages of the disease.

#### THE EXPERIMENTAL PRODUCTION OF GENERAL PARALYSIS IN RATS.

Through the kindness of Dr. Leatham, Bacteriologist of Charing Cross Hospital, I have been able to observe the result of some feeding and inoculation experiments on white rats. These were carried out in the laboratory of Charing Cross Hospital by Dr. Leatham, who on the death of the animals forwarded them to me for examination.

The organisms used in the experiments were obtained—(a) from the blood *post mortem*; (b) from the genito-urinary system of cases of general paralysis. Seven rats have been examined which have died after the course of feeding and nine which were subjected to inoculation. The latter were inoculated twice in the early part of August, 1907, with 0.25 c.c. emulsion of a 24 hours' agar culture. All died between the dates of 7th November and 2nd December, 1907, having survived about three to four months from the date of the first inoculation. In the feeding experiments each of the animals received twice weekly 0.5 c.c. of an emulsion of the diphtheroid organisms mixed with its food. The duration of life from the commencement of feeding was three to four months. Control animals remained healthy. The fact that practically all the animals subjected to the experiments died, while the controls remained healthy, suggests that the former succumbed to the toxic action of the organisms. This, however, is no proof of the specificity of these organisms in general paralysis; and sections of the brain showed no changes suggestive of that disease. Cultures were taken from the

tissues of the animals after death, but diphtheroid bacilli were not demonstrable.

#### THE VALUE OF ANTISERA TREATMENT.

Dr. Ford Robertson has claimed for antisera prepared from his two types of diphtheroid bacilli valuable curative and diagnostic properties. Of the use of this material I have no personal experience.

It is to be remembered that beneficial results of a more or less transitory nature have from time to time been advocated from the employment of other remedies such as anti-diphtheric serum, defibrinated blood withdrawn from a case of general paralysis and inoculated into another; fibro-lysin in a case of locomotor ataxia, etc. Moreover, remissions in the course of this disease may be of such duration as to simulate recovery and give rise to false impressions as to the value of any particular line of treatment which is being adopted. I hold it, therefore, to be wise to await a more extended use of this serum before it is universally accepted as a specific for general paralysis. With regard to the diagnostic value, the author states that whether the serum be given by the mouth or hypodermically, the rise of temperature which follows it is characteristic and, in his opinion, diagnostic. Now it is well recognised that general paralytics are frequently the subjects of irregular pyrexia produced by the varied complications to which they are liable. It would have been advisable, therefore, to have clearly stated that every precaution had been taken to ensure that the patient had been entirely free from any pyrexia for some days previous to the inoculation. In regard to the control cases it is stated that: "In none of these did any specific reaction occur after mouth administration, and any rise of temperature subsequent to injection could readily be explained by other factors." Explanation as to what these factors were is certainly desirable if the importance of the reaction is to be fully appreciated.

In conclusion I would like to draw attention to a recent publication of Dr. A. Marie. This writer states that as the result of a visit to the Morningside Laboratory in 1904 he was stimulated to follow up the researches of Ford Robertson. Bacteriological examination was first made of the urine and different tissues, notably the nervous system, cerebrospinal fluid and blood, but he was unable to find the *Bacillus paralyticus*. Cultures of the cerebrospinal fluid gave no result. In the blood he only found strepto-bacilli and staphylococci. Intra-peritoneal injections of the *Bacillus paralyticus* (sent to him) into white rats were unproductive. Experiments with regard to opsonisation and sero-agglutination in his hands produced anomalous results. In consequence he believes that the *Bacillus paralyticus* is not the specific factor in

general paralysis, but only an epiphenomenon and an element in the production of secondary infections.

#### SUMMARY.

With the opinion of Marie I am in entire agreement. That general paralytics are liable to secondary infections and complications is not disputed; moreover, it is possible that diphtheroid bacilli may play some part in these secondary infections and that the use of an anti-serum prepared from such bacilli may be attended with transitory beneficial effects.

The assumption, however, that a particular group or groups of diphtheroid organisms act as the specific factor in the production of general paralysis is unwarranted and has not yet been substantiated by any published research.

In conclusion, I desire to thank Dr. F. W. Mott for the interest he has taken in the work and for his many suggestions. I am also indebted to Dr. G. F. Barham and Dr. W. S. Hughes, who kindly obtained for me a large amount of material in the wards.

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#### ADDENDUM.

Since the above article was written, Dr. Hamilton Marr has recorded the results of a bacteriological examination of the cerebrospinal fluid of 53 cases of general paralysis. In no single instance did he succeed in cultivating a bacillus or any other organism from the fluid.



PLATE I

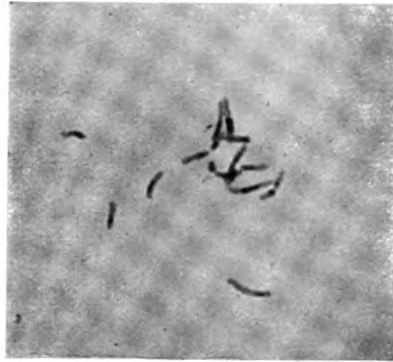


FIG. I.

Diphtheroid organism isolated in pure culture from the blood of a general paralytic (*post-mortem*). Blood serum, 24 hours' growth. Mag. 1,500.

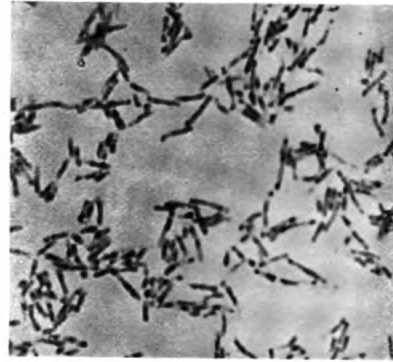


FIG. II.

Same organism as Fig. I. after several sub-cultures on Agar. Mag. 1,500.

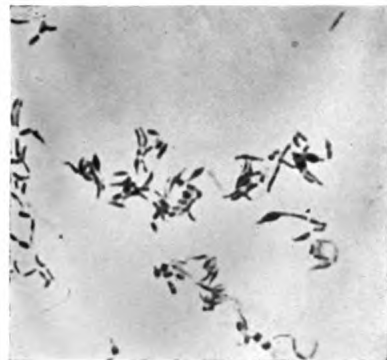


FIG. III.

Diphtheroid organism (Fig. II.) after 24 hours' exposure to the undiluted serum of a general paralytic. Mag. 1,500.

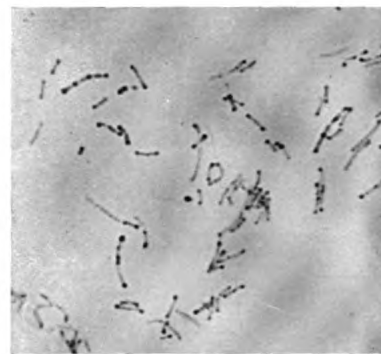


FIG. IV.

Diphtheroid organism (Fig. III.) after re-cultivation for 24 hours on blood serum. Mag. 1,500.



FIG. V.

A diphtheroid organism isolated from the urine of a male general paralytic during life. Blood serum, 24 hours' growth. Mag. 1,500.

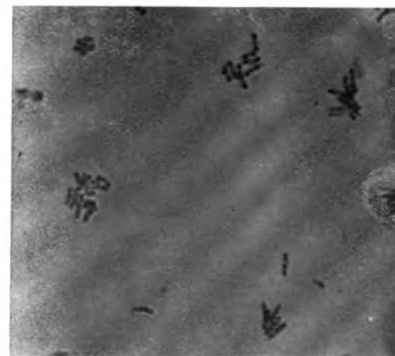


FIG. VI.

A diphtheroid organism isolated from the urethra of a case of senile mania during life. Blood serum, 24 hours' growth. Mag. 1,500.

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PLATE II.

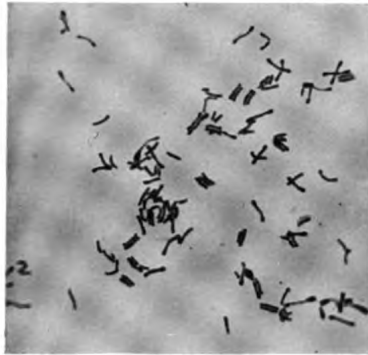


FIG. VII.

A diphtheroid organism isolated from the stomach of a general paralytic *post-mortem*. Blood serum, 24 hours' growth. Mag. 1,000.

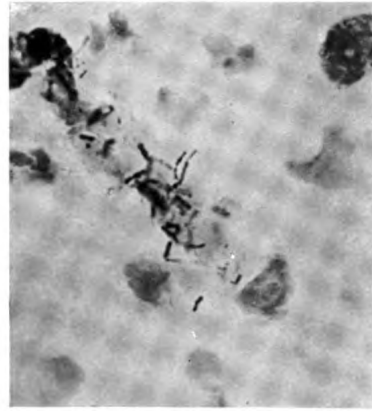


FIG. VIII.

A smear preparation from the cortex of a female general paralytic (one hour after death). Mag. 1,000.

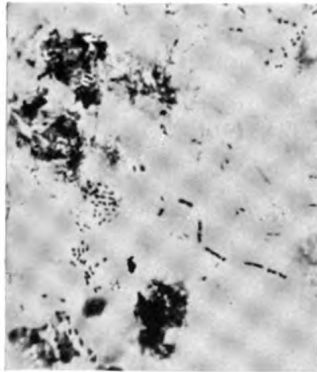


FIG. IX.

A smear preparation from the cortex of a general paralytic (22 hours after death). Mag. 1,000.

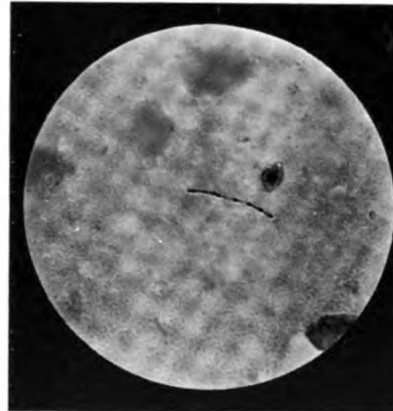


FIG. X.

A smear preparation from the cortex of a general paralytic. Same case as Fig. IX. Mag. 1,000.

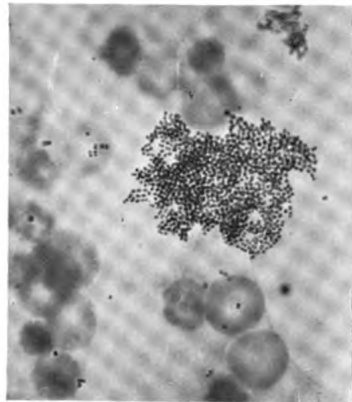


FIG. XI.

Growth in bouillon from the circulating blood of a general paralytic.

This organism was also obtained in pure culture *post-mortem* from the blood of same case. Mag. 1,000.

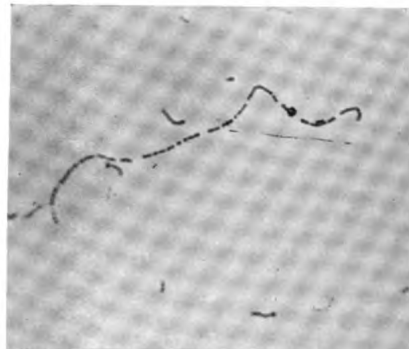


FIG. XII.

The same organism as shown in Fig. XI. Film made from the water of condensation of an Agar tube after transplantation from broth. Mag. 1,000.



PLATE III.



FIG. XIII.

Colony of a Kleb's-Löffler bacillus on Agar plate (76 hours). Compare margin with that of the colonies shown in following four figures. Mag. 5.

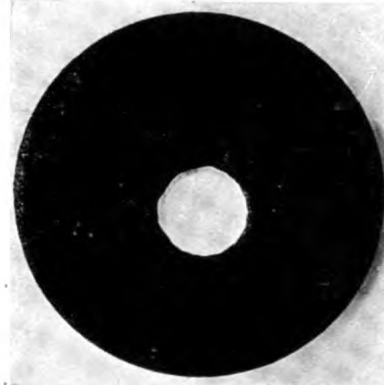


FIG. XIV.

Colony of a diphtheroid organism (same as Fig. I.) on Agar plate, 76 hours. Mag. 5.

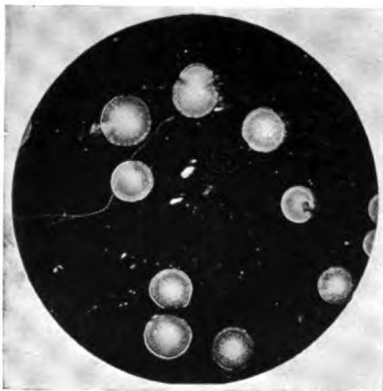


FIG. XV.

Colonies of a diphtheroid organism on Agar plate, 76 hours, from the urine of a general paralytic (same organism as Fig. V.). Mag. 5.

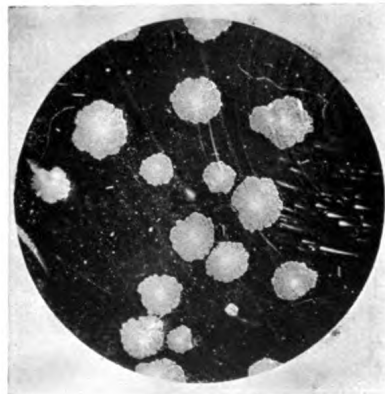


FIG. XVI.

Colonies of a diphtheroid organism on Agar plate, 76 hours, from the urethra of a general paralytic. Mag. 5.

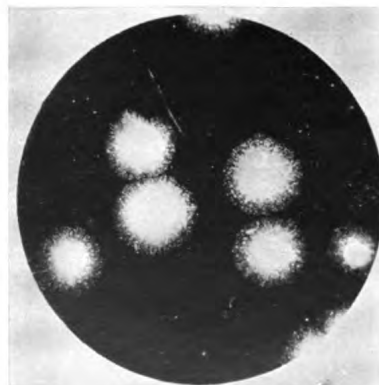


FIG. XVII.

Colonies of a diphtheroid organism on Agar plate, 76 hours, from the urethra of a case of simple mania. Mag. 5.



PLATE IV.

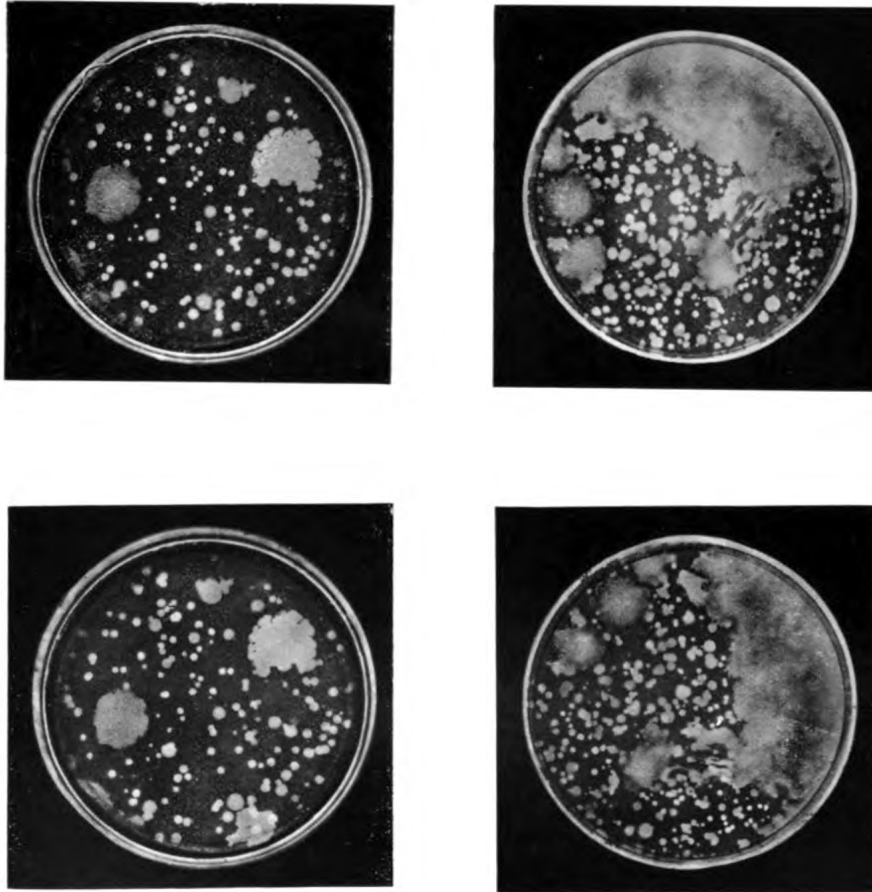


FIG. XVIII.

Photographs of Agar plates exposed for 15 to 20 minutes to the air of the general paralytic ward during the taking of blood cultures. Four-ninths original size.  
(To illustrate one of the liabilities to external contamination during this procedure.)





## HEMORRHAGE INTO THE SUPRARENAL CAPSULE.

By J. P. CANDLER, M.A., M.D. (CANTAB.), D.P.H.

The object of the following paper is to record two cases of hæmorrhage into the suprarenal capsule which were recently found on the *post-mortem* table of the London County Asylum at Claybury within three months of each other. The second of these cases is of especial interest in that the patient showed symptoms pointing to some obscure abdominal trouble shortly before death:—

CASE I.—*Bk. xii., Fol. 7.* W. J. L., a widower, was admitted to the Asylum on the 24th of November, 1906, and died March 6th, 1908.

He is described on admission as being a poorly nourished, miserable old man of 72, suffering from senile dementia, and in poor health and condition.

His physical state on admission is described as follows: "Tongue furred, edentulous. Reduplicated first sound at apex of heart. Complete arcus senilis. Oedema of feet."

He gradually became more feeble, and on the 5th of March, 1908, he had a syncopal attack.

He was put to bed and examined. His pulse rate was 62 per minute, and very feeble. There was evidence of commencing lung consolidation. The patient never rallied, and died on the following day.

The *post-mortem* examination revealed the presence of generalised arterio-sclerosis, granular kidneys, and cardiac enlargement. There were several old cerebral softening-situations in the basal ganglia, and also scattered over the cerebral cortex. The lungs were congested and oedematous, and in places were consolidated.

The left suprarenal capsule was disintegrated. The right was enlarged to the dimensions of a walnut, and on section was found to be filled with recent blood clot. (*Vide* Fig. I., Plate I.).

A microscopic examination was made of the various tissues to confirm the *post-mortem* findings. The medullary portion of the suprarenal capsule had been entirely replaced and destroyed by a recent hæmorrhagic extravasation.

This, so far as could be seen, was confined to that region and had not invaded the cortical portion of the capsule. The cells, however, in this region had nearly all undergone a necrotic change.

A microscopic examination of the kidneys showed a very marked degree of interstitial fibrosis.

CASE II.—*Bk. xi., Fol. 140.* I. B. H., male, aged 71, was admitted to the Asylum on December 24th, 1906, and died December 19th, 1907. This patient

also was the subject of senile dementia. His physical condition was extremely feeble. The following details of his last few weeks of life are of interest:—

On November 20th, 1907, he was seized with a sub-acute attack of diarrhœa, from which he recovered.

On December 13th he fell as he was being assisted in from the airing court; an attendant partly broke his fall, but he sustained an abrasion over his right eye.

On December 17th the patient had a kind of syncopal attack. Pulse rate 100, and of fair tension.

On December 18th he had a temperature of 102.6° and signs of broncho-pneumonia. He was apparently suffering from severe abdominal pain, for he groaned repeatedly and drew up his knees. The abdomen was distended and resonant on percussion, but there was dulness in the flanks. The bowels were confined. Patient died on December 19th.

At the *post-mortem* examination there were found general arterio-sclerosis and some cardiac enlargement, with increase in density of the renal tissue. There was a patch of old yellow softening in the right cerebral hemisphere. There was marked purulent bronchitis and hypostatic pneumonia.

Both suprarenal capsules were found to be very much enlarged, and on section were filled with clot of the colour and consistency of recently shed blood (*vide* Fig. II., Plate I.). The right capsule was larger than the left, being 4 cm. in length, 3 cm. in width, and 2 cm. in breadth. There was no extravasation of blood into the periadrenal tissue, or into the peritoneum.

Microscopic examination showed that in the case of both capsules the hæmorrhage was mainly situate in, and had completely destroyed the medullary portion. The cortical part showed a large number of very distended capillaries and some extravasation of blood. The cells in this region had undergone a considerable degree of necrotic change.

The kidneys showed a marked degree of interstitial fibrosis.

The discovery of these two cases induced me to examine the *post-mortem* registers in order to ascertain the frequency of visible hæmorrhage into the suprarenal capsule in the insane, as shown by the records of this institution, and to note in how many cases symptoms had been present which pointed to the existence of any abdominal trouble prior to death. I have therefore inserted in tabular form a list of all cases of suprarenal hæmorrhage out of a total number of 1,926 *post-mortem* investigations held on all forms of insanity.

From a perusal of the literature it would appear that hæmorrhage into the suprarenal capsule may occur as the result of (*a*) active or (*b*) passive congestion. The former variety appears to be more prevalent in young children and in the still-born, occurring in about 45 per cent. of necropsies, according to Arnaud. Dr. Still, however, only found four cases of suprarenal hæmorrhage in 3,793 necropsies on children under 12 years of age.

According to Dr. Spencer, injury at birth may be responsible for a large number of cases in the newly-born. In young children the disease



the post-mortem table at the London  
 isive. Total number, 1,926 (males, 937;

3. Other pathological conditions present  
 in the body, &c.

the	Vascular degeneration; coronary arteries calcareous; cortical softenings; renal fibrosis; cardiac hypertrophy.
kidney liver	Aneurism of aorta; vascular de- generation; adherent pericar- dium; bronchitis and emphysema.
chitis pneu-	General paralysis of the insane; scars of old syphilis; papilloma of the bladder with cystitis; a patch of dense pearly fibrosis in the aorta; kidneys congested.
nonia rally-	Pulmonary tuberculosis; scattered areas of early atheroma and pearly white fibrosis in the aorta; kidneys apparently quite healthy, but some slight increase in density.
into leap-	Purulent bronchitis; hypostatic pneumonia; cerebral softening; general arteriosclerosis; granular kidneys.
nonia re.	General arteriosclerosis; granular kidneys; multiple cerebral soft- enings.
; hy- stion f the	? Myxœdema; a moderate amount of scattered fibrosis generally distri- buted through the aorta; kidneys congested.
dural acute	A moderate degree of atheroma. Granular kidneys, some cardiac hypertrophy.
ncho- and effu- side. of	Nil noteworthy.
onia..	Moderate degree of atheroma. Granular kidneys.

as before death hæmaturia commenced and  
 very collapsed state.

final trouble were noted on the day before  
 elsewhere.)

and rapid, but no murmurs.  
 t. ; females, 0.4 per cent.).

may supervene during the course of many acute infections, especially diphtheria, or may occur quite suddenly in a previously healthy child, accompanied by purpuric eruption, fever, and sometimes convulsions, suggesting the onset of some intense infection. That this acute condition is due to some toxic origin is rather favoured by the results obtained by the experimental injection of various micro-organisms into animals, *e.g.*, diphtheria bacilli (Roux and Yersin), bacillus pyocyaneus (Langlois and Charrin), Friedländer's bacillus (Roger), whereby congestion of the gland with engorgement and effusion have resulted.

That a similar condition may occur in adults is shown by a case, reported by Dr. Andrewes, of a medical man, aged 53, who was suddenly seized with profuse hæmorrhagic purpura and died in a few hours. A blood examination showed the presence of meningococci. *Post mortem* both suprarenals were in an intensely hæmorrhagic condition, whilst, in addition, there were cutaneous and subarachnoid hæmorrhages.

The characteristic features of these hæmorrhages into the suprarenal capsule are stated by Dr. H. D. Rolleston to be the sudden onset with fever, pain in the hypochondrium radiating into the loins, convulsions, vomiting, diarrhœa, and later tympanites, collapse, and death within 48 hours.

In adults, hæmorrhage into the suprarenal capsule is much less frequent. According to Leconte it occurs once in every hundred cases, but Arnaud thinks that this rather under-estimates the frequency.

Out of a total number of 1,926 *post mortems* at Claybury, visible hæmorrhage was found in 10 cases (six males and four females), giving a frequency of 0.5 per cent. (*Vide* Table.)

Generalised atheroma is a fertile cause of hæmorrhage; consequently, age and senility are predisposing factors. As will be seen from the table only three cases of suprarenal hæmorrhage occurred under the age of 40, and two of these were cases of general paralysis of the insane. In the remaining cases a greater or less degree of vascular degeneration was present.

The proportion of cases is stated to be greater in the male sex (the appended table shows a percentage of 0.6 per cent. in males as against 0.4 per cent. in females). This may be explained by the greater liability of the male sex to degenerative changes in the vessels. Predisposing factors will be found in all the causes which promote venous engorgement in the general or abdominal circulation, such as cardiac and respiratory embarrassment, pulmonary tuberculosis, especially noted by Arnaud, cerebral affections accompanied by prolonged coma, etc.

The co-existence of renal lesions, especially of interstitial nephritis, with hæmorrhage into the suprarenal capsule has been noted by Letulle

and Pilliet. A reference to the table of cases in this paper will show the marked association of suprarenal hæmorrhage with arterial degeneration and granular and fibrotic kidneys. Phlebitis of the capsular veins and thrombosis of the renal veins have also been noted as being associated with this lesion (Arnaud, Parrot, Droubaix).

*Symptomatology.*—The symptoms are vague and indefinite. Arnaud has classified them as follows:—

(1) Cases exhibiting signs of peritonitis or of intra-abdominal hæmorrhage capable of being diagnosed and treated during life.

The author mentions two cases which were signalised by painful crises, returning at intervals, situated in the epigastrium or in the region of the kidney. The crises were accompanied by vomiting. Mattei has reported the case of a man, aged 60, with an ulcer of the leg, who shortly after admission was seized with very acute pain in the lower part of the abdomen and died in 24 hours. No other lesion was found *post mortem* except hæmorrhage into the suprarenal capsule.

Of the series of ten cases recorded in the accompanying table, one case only presented symptoms of abdominal pain, with a somewhat distended abdomen resonant on percussion, and dullness in the flanks. The symptoms are unfortunately very obscure and liable to be confused with other forms of acute abdominal trouble, especially, perhaps, with hæmorrhage pancreatitis. This case, however, shows the importance of remembering the possibility of suprarenal hæmorrhage when the precise nature and situation of some acute abdominal trouble cannot be located.

(2) Hæmorrhage giving rise to symptoms of suprarenal insufficiency, such as anæmia, muscular weakness, prostration, loss of weight, and diarrhœa (without bronzing of the skin), and the author thinks that it would be well to place by the side of the classic malady of Addison a clinical chapter on "Suprarenal Syndromata *not* Addisonian."

To diagnose a case of hæmorrhage by these symptoms alone would, I think, be an impossibility. Many cases of insanity exhibit the symptoms of anæmia, muscular weakness, prostration, and loss of weight. With regard to diarrhœa it is interesting to note that one of the cases recorded had an attack of sub-acute diarrhœa one month before death, but to assign this solely to suprarenal insufficiency would be unjustifiable, especially in an asylum where cases of simple diarrhœa and institutional dysentery frequently occur.

Reference to a paper by Dr. F. W. Mott and Professor Halliburton on "The Suprarenal Glands in Nervous Diseases" shows that suprarenal insufficiency is common in the insane. In 71 cases of insanity in which the suprarenal glands were examined chemically and physiologically, 46.4 per cent. gave no reaction or only a faint coloration with Vulpian's

ferric chloride test for adrenalin, and 36.6 per cent. occasioned a fall of blood pressure when injected into rabbits. It is of interest that one of the cases of hæmorrhage recorded in the Table (viii., fol. 109) was among the series of suprarenal glands tested in this way, and both chemically and physiologically showed a deficiency of adrenalin.

(3) Hæmorrhage accompanied by predominant nervous symptoms. These are cases of the utmost importance.

They are characterised by a rapid and unexpected fatal termination preceded or accompanied by grave nervous phenomena, such as convulsions, delirium, or coma without paralysis. For example, as Arnaud states: "A person in full health or during the course of some illness of minor importance is suddenly struck down with syncope or coma, with or without convulsions, and succumbs after some hours or days without anything being found to explain the cause of death, the only lesion *post mortem* being hæmorrhage into the suprarenal capsules. He reports such a case in a man, aged 36, who was brought into hospital in an unconscious condition, death occurring in 48 hours without any evidence being forthcoming as to the nature of his malady. Hæmorrhage into the suprarenal capsules was the only lesion discovered *post mortem*."

It is of interest to notice that three of the cases which I have recorded had a severe syncopal attack 24 to 48 hours before death, though it must be acknowledged that this might have been due to other causes.

Such cases, Arnaud says, are not uncommon. He has met with 15 similar instances in his observations upon 79 cases of hæmorrhage into these organs.

The sudden and rapid death is attributed to the damage done to the adjacent abdominal sympathetic plexus by the hæmorrhage into and distention of the suprarenal capsule.

Vigorous and Collett have recorded a case of bilateral hæmorrhage into the suprarenal capsule in a general paralytic, aged 50; the symptoms noticed being those of profound coma followed by death. This case is, so far as they are aware, the first case recorded in a general paralytic. Out of the ten cases recorded in these statistics, two occurred in cases of general paralysis. Hæmorrhages occurring in the course of diseases of the nervous system have also been recorded in chronic meningitis with cerebral congestion, epilepsy, senile dementia, cerebrospinal meningitis, and hemiplegia from cerebral hæmorrhage.

(4) Cases which give rise to no appreciable symptom, and are not capable of being attributed to a capsular lesion.

The condition of the suprarenals is only found at necropsy, associated with some other pathological condition which of itself has been sufficient to cause death. Several of the cases which I have recorded must be included in this group.

Lastly, there is a group of cases in which death has occurred and nothing else has been found *post mortem* beyond hæmorrhage into the suprarenal capsule. Dr. Langdon Brown, in an analysis of 4,110 necropsies at St. Bartholomew's Hospital, reports three such cases. This suggests that death and even sudden death may occur from such a hæmorrhage alone, without giving rise to any symptoms. Such a case is recorded by Dr. Goodhart in a man suffering from emphysema, who died suddenly and without apparent reason, hæmorrhage into the suprarenal capsule being the only lesion found.

#### CONCLUSION.

The importance of hæmorrhage into the suprarenal capsule lies in the fact that such a lesion may occur, giving rise to obscure abdominal or nervous manifestations difficult of diagnosis, and may even be a cause of death without any appreciable symptoms whatsoever.

I wish therefore to emphasise the necessity of remembering that such a condition can occur, and further to urge the importance of carefully examining the suprarenals in all cases where death has occurred without any lesion being found in other parts of the body of sufficient gravity to account for death.

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PLATE I.



FIG. I.  
Hæmorrhage into right suprarenal capsule. (Case I.)

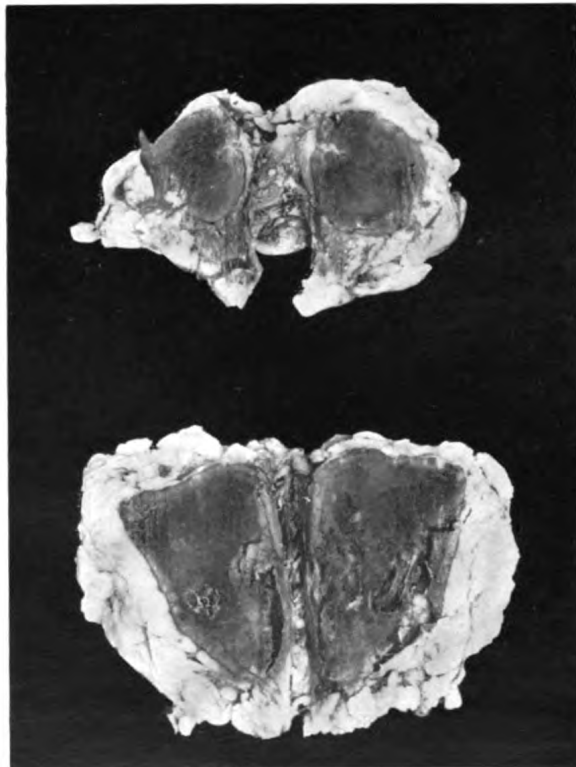


FIG. II.  
Hæmorrhage into both suprarenal capsules. (Case II.)



# THE PHYLOGENESIS OF THE PALÆO-CORTEX AND ARCHI-CORTEX COMPARED WITH THE EVOLUTION OF THE VISUAL NEO-CORTEX.

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While studying the phylogenesi8 of the rhinencephalon and its connections I was struck by the great resemblance which its cortical layers show compared with different stages in the progressive development of the visual cortex as described by Dr. Mott, and I thought a short communication thereon might contribute to our knowledge of the principles underlying the development of the central nervous system.

Before trying to make out these structural analogies I will describe the progressive evolution of each form of cortex separately, and will first explain what is meant by the expression *palæo-cortex*.

As is known Elliot Smith has distinguished two territories in the pallium of mammalia, the *archi-pallium* and the *neo-pallium*, of which the first is older, being already present in reptiles, where a *neo-pallium* at his time had not yet been demonstrated. The characteristic feature of the *archi-pallium* is, that its cortex, the *archi-cortex*, receives tertiary olfactory fibres, which bring olfactory impressions to it from the secondary olfactory centres, the *neo-cortex* receiving tertiary impressions of non-olfactory character, acoustic and visual impressions, and impressions of general and special body sensibility. The different sorts of pallium, however, are not yet exhausted by these two types, as in the lower vertebrates, in cyclostomes and selachians, the mantle only consists of nervous substance, which does not receive tertiary but only secondary olfactory fibres, and the same is the case with the greater part of the dorsal nervous wall, which covers the lateral ventricle in amphibia.

This nervous substance, in order to distinguish it from the sub-ventricular grey substance, should be called *palæo-pallium*.\*

\* This *palæo-pallium* is also present in Ganoids and Teleosts, but poorly developed and is bent outward (latero-ventrally) instead of inward (medio-dorsally). The primary, medial epistriatum of these fishes replaces a great deal its functions. For further details see the paper published by Mr. Theunissen and myself on the Phylogenesi8 of the Rhinencephalon.

It is the oldest nervous mantle occurring in vertebrates, and in higher vertebrates is pushed ventrally by the great development of the archi-pallium and especially of the neo-pallium.

Just as in the pallium there can be distinguished three territories according to the connections which they exhibit, so the cortical structures occurring in them should be distinguished, according to the same principle, into a *palæo-cortex*, *archi-cortex* and *neo-cortex*, of which the first forms what is often called the cortex olfactoria, cortex lobi olfactorii, cortex lobi piriformis, etc., which names are better replaced by the expression *palæo-cortex*, which indicates its phylogenetic position.\*

The place which this latter cortex occupies in lower vertebrates is, perhaps, strange to our general conception of cortex as it first appears in its most distinct form in the subventricular wall of the brain and not in the palæo-pallium, where the palæo-cortical arrangement, though present, is not nearly as typical as in the ventral grey substance.†

Fig. 1 shows the structure and position of the typical palæo-cortex of a *Selachian*, scyllium canicula (in many sharks—*Galeus canis*, *Centrophorus*, *Spinax*—it is present in exactly the same form). It is evident that it consists of two layers (I do not speak of the molecular layer in this short note): a very large and distinct layer of granular cells (Fig. 2) and underneath this (*i.e.*, nearer the ventricle) a layer which contains amongst others larger cells, which sometimes are pyramidal in form, in other parts exhibit very different outlines (Fig. 3): polymorphous cells. In and above the granular layer secondary olfactory fibres end and underneath it, mostly from the infragranular cells, tertiary tracts originate (part of the tr. olfacto-habenularis and of the tr. olfacto-hypothalamicus rectus et cruciatus).

As is known in *amphibia* the ganglion cells remain for the greater part in the stage of the "Mantelschicht" of *His*; they do not or hardly ever emigrate from the ventricular ependyma, near which they keep crowded together. Distinct cortical layers are not formed in the palæo-pallium of these animals. So the next type of a well-differentiated palæo-cortex is found in the *reptiles* (Fig. 4), where it lies in the ventral and lateral wall. The dorsal and medio-dorsal part of the pallium contain the archi-cortex, the structure of which will be described hereafter. What has to be noticed here is that a continuation of the lateral cortex extends a certain distance over the pars ammonica of the archi-

\* The expression mostly used until now: cortex olfactoria, is not right because the archi-cortex is also a cortex olfactoria.

† In Teleosts and Ganoids a real cortical structure does not occur, because the whole tendency of these brains, where a massive (primary) epistriatum replaces the greatly reduced palæo-pallium, is to contain the greatest quantity of grey substance with as little superficies as possible, and so all cells are more crowded together.

cortex, which may be called *superpositio lateralis*, and that fibre tracts from the lateral cortex go into the archi-cortex: fibræ olfacto-hippocampales externæ, which are partly associative fibres.

A closer study of the lateral cortex shows that it contains many more pyramidal cells than the palæo-cortex of the selachians, and that these pyramidal cells (Fig. 5) are found chiefly in the dorsal and the caudal part of it, whereas cells of a granular, stellate and fusiform character, closely crowded together, are found in its frontal and basal part (Fig. 6), although some of them are also present in the other parts. This arrangement can be easily understood if we know that the secondary olfactory fibres finish mostly in the frontal and basal part of this cortex, whereas the greater tertiary olfactory tracts take their origin in more dorsal and caudal parts, in the latter of which caudal descending connections (with the hypothalamus and ganglia habenulæ) also originate.

An important thing to mention here is that the upper part of the lateral cortex layer has certainly already a neo-cortical character, as is proved by the fact that a certain amount of fibres, originating in a neothalamic nucleus of the fillet (nucl. rotundus: chiefly n. med. thalami of mammals) end in it. As the nucl. med. thal. (and also the nucl. rotund.) receive trigeminal fillet-fibres, it results that the first neocortical tactile region is one of oral sensibility (just as the first neostriatum). The associative part of the dorso-lateral fibres are consequently partly trigeminal-hippocampal fibres (besides olfacto, hippoc. fibr.). This first neocortical region is directly continuous with the palæo-cortex itself.

The most characteristic feature of the palæo-cortex itself is that the granule-like cells are less in number and chiefly restricted to the fronto-basal part, whereas the pyramidal cells, greatly augmented, are chiefly found in more dorsal and caudal parts, although they are found also under the granular layer in the fronto-basal part. So the cells of different type are not as much arranged under each other as next to each other, side by side.

To comprehend the palæo-cortex of *mammalia*, Professor Livini and I studied marsupials, of which it is necessary to say a few words about the neo-cortex.

The latter is formed between the archi-cortex and the palæo-cortex, originating from the palæo-cortex, with which it is still entirely continuous in the reptiles. By its enormous development the archi-pallium, with the archi-cortex, is pushed medialwards, and is rolled together. (Compare also Elliot Smith and Gius. Levi.) The palæo-cortex is pushed ventralwards, and occupies a great deal of the base of the brain and a small part of its lateral aspect; so its place can be hardly still called palæo-pallium, as it is located for the most part under the striatum, but

its cortex is homologous with the palæo-cortex of the reptiles; in contradistinction to the reptiles the palæo-cortex in mammalia is sharply distinguished from the neo-cortex by a deep fissure: the *fissura rhinalis lateralis*.

So, the archi-cortex and palæo-cortex are greatly removed from each other by the extensive growth of the neo-cortex and the only place where they are not separated from each other by neo-cortex in the mammalian brain is the occipital pole of the brain, where the *superpositio lateralis*\* is very striking (Fig. 7) and where the *fibræ olfacto-hippocampales externæ*—in the reptiles distributed over the whole extent of the lateral wall—for the greater part are packed together in some thick bundles, which now form the *tr. spheno-ammonicus* of Cajal.

It is evident from this that the occipital part represents a region, found in the dorsal and caudal part of the palæo-cortex of reptiles, which is confirmed by its structural features, as its cells, arranged in four to six rows (of which the upper and lower one contain the most of them), are nearly all pyramidal cells, or at least such of which the type shows that they are cells with long axis cylinders.

The granular layer—as in the reptiles—is chiefly confined to the fronto-basal region of the palæo-cortex (Fig. 8), where it is very pronounced as well in the form of its cells as in their close arrangement† (Fig. 9). Under it there is a distinct layer of very large pyramidal cells (Fig. 10). In this region a great deal of secondary olfactory fibres end (granular cells) and in the deeper layer tertiary olfactory fibres to the archi-cortex begin (pyramidal cells).

If we compare the different forms of palæo-cortex, from the selachians to the mammalia, we see that its progressive evolution goes together with an increase in number of the pyramidal, larger cell-type. In the selachians the few larger cells are chiefly located under the very extensive granular layer, as is found still in the baso-frontal part of the palæo-cortex of reptiles and mammalia, but in the greater part of the mammalian palæo-cortex and in the reptilian the greatly augmented pyramidal cells are also present next to the granular layer, more side by side.

For the study of the phylogenetic development of the archi-pallium and *archi-cortex* we have to begin with the *amphibia*, where such a cortex first occurs.

\* The *superpositio lateralis* is also visible between the rest of the Ammonformation and the subiculum, resp. the gyrus fornicatus, but less typical. According to my opinion the *fibr. olf.-hipp. ext.* contain different fibres, which bring impressions from different regions to the archi-cortex of which in reptiles the palæo-cortical connection (packed together in mammals in the *tr. spheno. amm.*) prevails. In mammals also fibres from the gyrus fornicatus occur in this system.

† I cannot understand how *Cajal* can deny the presence of granular cells in the palæo-cortex of mammalia. As my drawing shows there are many of them, as also has been stated by *Calléja* (l.c. p. 33).

The *primordium hippocampi*, as one might call the poorly differentiated archi-cortex of these animals, is, however, too primitive in its structure for a distinction in layers to be possible.

Granular cells, or rather cells of little differentiated character, form the greater part of it, and are mixed with some multipolar cells, which probably send out the little fornix and a part of the commissura pallii of these animals.\* In *reptiles*, however, a very distinct division in layers is visible (Fig. 4).

The granules packed together in a dense row of very small cells (Fig. 11) occupy the whole mesial wall of the pallium and a small part of the dorsal. The rest of the dorsal wall contains much larger cells of a pronounced pyramidal type (Fig. 12), which are not at all crowded together but rather at some distance from each other.

The first layer (A) is the fascia dentata (c.f. Brill, Gius. Levi) and the latter (B) the ammon-formation, the cells of which have long axis cylinders that can be traced in the fornix, in the tr. cortico-habenularis and in the commissuræ pallii anterior and posterior (which form the psalterium of these animals).

In consequence of the fact that the tertiary olfactory fibres reach the archi-cortex for a great part (directly or indirectly) through the molecular layer, the fascia dentata has a somewhat more superficial position than the ammon-formation, and, though in some reptiles these layers are continuous over the whole extent of the dorsal surface, in most ophidia and sauria they are separated more or less, and the ammon-formation extends a short distance under the fascia dentata (*superpositio medialis*) as well as under the lateral cortex (*superpositio lateralis*). On an average the ammon-formation lies much nearer the ventricular ependyma than the fascia dentata does, and its cells are much less numerous than those of the latter, as is seen: (1) From the length of the ammon-formation, compared to the length of the fascia dentata, about as 1 :  $1\frac{1}{2}$  in *Boa constrictor*; (2) from the fact that the cells of the ammon-formation are much less packed together. It is difficult to estimate the exact relation between the number of granular cells and the number of pyramidal cells, but there are at least four times more of the former than of the latter.

If we compare with this reptilian archi-cortex the archi-cortex of the kangaroo-rat (Fig. 13) we find an enormous increase of the ammon-formation the length of which, compared to the length of the fascia dentata, is about as  $5\frac{1}{2}$  :  $2\frac{3}{4}$ . Moreover, the cells of the ammon-formation (Fig. 14) are nearly as much packed together as the cells of the fascia

\* A striking difference with the cells in the palæo-pallium is that those in the archi-pallium are much further emigrated from the ventricular ependyma, and so form the beginning of a real cortical layer.

dentata (Fig. 15), and the cells of the ammon-formation extend much nearer to the ventricle than they do in the reptiles. So, whereas in the Boa the ammon-formation was the smaller of the two, in *Hypsiprymnus* it is by far the larger, and contains more cells than the fascia. This is accompanied by an enormous enlargement of the fornix and the psalterium.

Another difference between the archi-cortex of reptiles and marsupials is the large development in the latter of what in analogy to Mott's nomenclature I have called the olfacto-psychic cortex, the "Anlage" of the gyrus fornicatus and the caudal subicular region, the olfactory character of which is proved by the tertiary olfactory fibres, which reach it through the septum\* and because it receives a part of the fibræ olfacto-hippocampales. The externæ (tr. spheno-ammonicus) psychic, *i.e.*, higher associative character of this region is proved: (1) by the enormous amount of pyramidal cells which extend into the molecular layer and so partly have to be considered as supragranular pyramids; and (2) by the great number of association fibres, which connect it with the adjoining neo-cortex and which, with the tertiary fibres above-mentioned, constitute the cingulum S. Str. (also called cingulum gyri-fornicati, better called cingulum limitans, because it separates the archi-cortex from the neo-cortex). This olfacto-psychic cortex is connected with the other hemisphere by callosal fibres and not by the psalterium.

Surveying the evolution of the archi-cortex we find as characteristic features:—

- (1) A primary prevailing of the granular layer† (about four times more granules than pyramids: Reptiles);
- (2) The enormous increase in mammalia of the pyramidal layer (ammon-formation) which has projective and bilateral associative functions;
- (3) The formation in the latter of an olfacto-psychic centre with a great amount of pyramidal cells, which reach up to the molecular layer and so partly have to be considered as supragranular pyramids.

It is obvious that the fascia dentata represents the granular layer of other cortex forms, and equally sure that the ammon-formation represents the subgranular pyramids and polymorphous cells, because it lies nearer the ventricle and even partly extends under the granular fascia dentata (*c.f.* fig. 4 and 13).

Comparing these results with Dr. Mott's concerning the visual cortex.

\* They run together with the cingulum (limitans), already present in reptiles, but, just as the olfacto-psychic centre, hardly indicated there.

† According to Tandler and Kantor this layer also appears first of all the layers in the ontogenesis of the reptilian forebrain.



we find that the palæo, archi- and visual neo-cortex correspond in so far as:—

(1) In the lowest degree of development the granular layer prevails in the palæo- and archi-cortex, and is also clearly developed in the lower types of visual cortex;

(2) With higher development the large pyramidal and polymorph cells, which constitute the sub-granular pyramids, become more numerous (compare for this Dr. Mott's drawing of a camel's visual cortex with the mole's).

(3) With further evolution, as well in the archi-cortex as in the visual-cortex a psychic centre of higher associative character is formed in which the granule-cells are greatly diminished, the pyramidal cells greatly augmented, and extend unto the molecular layer\* (compare for this Dr. Mott's description of the primate's visual cortex with my Fig. 13). So we find nearly the same principles as well in the progressive development of the palæo- and archi-cortex as in the progressive evolution of the visual neo-cortex.

In forma, however, there is a very striking difference, viz., the fact that, while in the visual and other forms of neo-cortex the different layers are located one above the other, they are—especially in the archi-cortex—located side by side, although the pyramidal layer of the ammon-forma is nearer the ventricle, a fact to which already Cajal and Taalman Kip have drawn attention. The very fact that in the archi-cortex the different layers are so far removed from each other is just the reason why the significance of each layer can be stated there so clearly.

It seems to me that this difference may be due to the economy in space, which is necessary in the neo-cortex, which is so enormously developed in mammals.

There is another question about which a few words might be said.

Dr. Watson, in his paper on the "Cortex of Insectivora," supposes the infra-granular polymorphous layer to have, besides motor function, an associative character of low order.

This is easily demonstrable for the sub-granular pyramids of the archi-cortex: the ammon-forma, because we know that the psalterium arises here, and the psalterium, as only containing bilateral associative fibres between two centres of the same quality (tertiary olfactory centres) has to be regarded as a relatively low associative system.

\* In the palæo-cortex, the homologue of this region—as far as concerns structural features—is found in the posterior region of the piriform lobe. The greater part of the pyramidal cells of that region constitute *fibræ-olfacto-hippocompales externae*, which are better concerned as tertiary olfactory fibres than as associative fibres, but there end near or in this region also *cingulum limitans* fibres, so the homology does not entirely fail. Moreover, we see that this cortex continues in the subiculum and the latter in the gyrus fornicatus.

On the other hand, it is true that the ammon-formation has given rise to the fornix and cortico-habenular tracts, and so has at the same time a projective character. Now fornix and psalterium get *nearly at the same time their myeline-sheaths*, which is also the case with the fibræ profundæ of Meynert\* and the neo-cortico-fugal tracts. This, combined with the fact that a great part of the largest pyramidal cells (Betz-cells) in the motor-cortex, which are generally considered as mother-cells of projection fibres, lie in the sub-granular layer, makes the above-mentioned supposition still more probable to me: that not only in the archi-cortex, but also in other cortices the deeper pyramids have as well a projection as an intra-regional association function.

In contradistinction to the sub-granular pyramidal cells, those of the supra-granular layer have a more *inter-regional* associative character connecting functionally different regions of the cortex, and, therefore, chiefly developed in those animals which lead a more advanced intellectual life, their number being not only dependent on the development of the special region in which they occur, but chiefly on the presence of other neighbouring or distant cortex-regions with which they are in connection.

This conclusion, drawn from Dr. Mott's and my own researches, has lately been confirmed in a most striking way by a small though most interesting article of Bing. Bing found, examining a deaf man's brain, that there was a reduction in the cells of the auditory cortex. This reduction, however, was almost entirely confined to the layer of infra-granular pyramids of which the depth was diminished to about three-fifths of the normal (a similar observation has been described by v. Monakow after lesion of the internal capsule). Recently, Winkler† showed me a brain of a deaf man, which exhibited exactly the same features as far as concerns its cortical layers. I believe that no fact is more able to prove the truth of the deductions above-mentioned than these, as they confirm entirely: (1) that the sub-granular layer depends in the first place on the local development of the sub-cortical system to which its region belongs, whereas the supra-granular layer is, in the first place, dependent on *inter-regional* associative qualities of neighbouring and distant cortical regions.

A few words might be added about the nature of the granular cells

\* Interesting for the difference between deeper intraradial associative fibres and the supra-radial associative fibres (Edinger) is also Kaes' observations (if it might prove to be constant) that the first prevail in the Chinese and Hindoo brain, whereas the latter were more numerous in an average European brain. It seems quite possible that "instinctive" or at least lower associations prevail more in the first than in the latter.

† Compare: G. Brouwer, Over doofstomheid en de acustische Canen. Inaug. dissert. Amsterdam. 1909.

in the brain-cortex. They belong, as is known, to the intercalary cells of Von Monakow, who pointed out their presence in nearly all parts of the central nervous system. Since he called special attention to them, their general occurrence has often been stated, and it is beyond doubt that their presence is of utmost importance.

In a paper upon the causes of formation of nervous tracts, I have pointed out that there are several good reasons to prove that a connection between different regions of the central nervous system is mostly caused by the sensory qualities of these regions: that even, for instance, the pyramidal tract of the forebrain does not descend to the spinal cord because the motor cells in the latter want stimulation, but because there is a functional relation between the sensory centres of the spinal cord and a sensory centre of the telencephalon. I further called attention to the probability that the granular cells of the central nervous system play the greatest rôle in neuro-bio-taxis, because, while in projection cells the nervous current is directly realised and led away, on the contrary, in the granular cells with short axis cylinder forming an intricate network the stimulation is kept within a certain region, and so this region acquires a great importance as an attractive centre for the outgrowth of axis cylinders and dendrites from other regions.

A fact is that the granule-cells, or cells with short axis cylinder, are very often the primary places which receive the long ascending\* or descending† tracts. The phylogenesis of the palæo- and archi-cortex demonstrates this law in a very striking way, as it shows that the small granule-cells in the cortex are always the first thing present, they are the primary constituent of every cortex, the receptory cells whereabout the long afferent (tertiary) tracts end (see Fig. 1). So, being primary in character, they are often present in a fairly large number even there, where their function for transmission of the nervous current on projection cells is not yet of great importance. A striking example of this is the fact mentioned by Zuckerkandl that in the dolphin, where no olfactory tracts are present the fascia dentata forms a "thick layer" of cells, and equally interesting is the fact that in the visual cortex of the mole, a nearly blind animal, the granular layer shows the best development. The same was the case in the deaf man's brain examined by *Winkler*, where the granule-cells did not show any reduction at all.

The efferent tracts and their cells, according to my results about the palæo- and archi-cortex, are formed only later, and no doubt they

\* A striking example is the ending of the sensory root-fibres in the oblongata and (less general) in the cord.

† A striking example is the ending of the pyramids in the cord and of the tecto-bulbar tracts in the oblongata.

take their origin from undifferentiated cells, which originally in their form and character come nearer the granules. An example of this seems to be given by the primordium hippocampi of Amphibia, where some cells, of which the perikaryon and the dendrites are exactly like those of granular cells, send out pretty long axis-cylinders, which pass in the commissura pallii to the other side.

From this point of view it is not astonishing if, during phylogenesis, we should not only find an augmentation of the pyramidal cells, but also a diminution of the granule cells in certain regions.

The latter cannot easily be stated in the archi-cortex, because the numbers above-mentioned, which show the relation between the granule cells and pyramidal cells in the archi-cortex of reptiles and mammals, may be due as well to an augmentation of the pyramidal cells alone (which, in this case, I think more probable) as to an augmentation of the latter and a diminution of the granule cells at the same time.

The phylogenesis of the palæo-cortex, however, supports this mode of evolution if we compare Fig. 1 to Fig. 4, where not only the augmentation of pyramidal cells is visible, but the diminution of granule cells is still more evident, and although in marsupials the granular-like layer in the fronto-basal part of this cortex is still very large, there are certainly much less than in the Selachian palæo-cortex, so that there really seems to be some evidence for the supposition that not only the augmentation of pyramidal cells, but also diminution of granule cells, at least in some regions, may be an attribute of further development during phylogenesis, a conclusion which seems to be in harmony with Brodmann's ontogenetic observations, though certainly in other regions further development is accompanied with an augmentation of the granules.

There is still another point about these intercalating cells to which attention may be drawn; the fact that these little granule-cells are sometimes present, where two long paths join, without being intercalated between the paths. An example of the latter is the formatio bulbaris, where granule cells can be found from the cyclostomes (Johnston) to the mammals, whereas the dendrites of the mitral-cells in the glomeruli olfactivi are in direct contact with the end branches of the fila olfactiva.

Apparently there are places where such an intercalation between the afferent and efferent tracts is either not necessary, and never has existed, or has gradually disappeared. This much is certain, that there are places where the granule-cells are nearly always intercalated between two long tracts (as f.i. between the sensory and motor-root of the VII.,

and between the sensory root of the IX. and X. and the nucl. ambiguus) and others (less in number) where they are not present as such.

Without presuming to be able to explain this difference, I desire to call attention to it, inasmuch as in the progressive development of the palæo-cortex we observe something analogous in the fact that not all the secondary olfactory fibres end around cells with short axis cylinders, which, as already pointed out, may be the case in a part of the archi-cortex.

It is not improbable that, in a region where the granules were originally abundant, in the course of progressive evolution they may change into larger stellate or pyramidal cells of projection systems. If their axis cylinder became longer\* their cell-body also would lose the small granular form, and then the afferent tracts would terminate directly around a projection cell. Similar results have been obtained by *Dr. Rondoni*, who worked in *Dr. H. Vogt's* department of *Edinger's* Institute, on pathological brains.

On the other hand, it might also happen that, when in a certain region of the central nervous system only one direction in the nervous current is possible, as in the bulbar formation, where associations with other regions are excluded, that a direct connection without intercalation is formed and the granular cells only form short paths of association between adjacent cells.

With our present knowledge, however, of the structural laws of the nervous system, this question cannot yet be explained with certainty, and the idea of this short communication is chiefly to point out the evolutionary principles of the palæo- and archi-cortex, their resemblance with those in the progressive evolution of the visual neo-cortex, as shown by *Dr. Mott's* work, and the character of the different cortical layers, which we may deduce from them.

Resuming my results, I may draw the following conclusions:—

(1) The granular layer in the cortex is primary in character, and has originally receptory functions. This can be proved phylogenetically and pathologically. Being primary in character, it shows a great constancy in being present, whether the afferent fibres are numerous or not. (It can enlarge, however, if the afferent tracts greatly increase.)

(2) The infra-granular layer, as already pointed out by *Watson*, has projection and intra-regional associative functions.† It increases phylo-

\* An example of this is seen in the development of the secondary epistriatum, which in some reptiles lies very near the palæo-cortex, and so has very short connections with it, whereas in mammals the same connections (with the nucleus amygdalæ) are very much longer.

† This does not exclude, of course, that they can receive (and often do receive) a certain amount of afferent fibres also.

genetically after the formation of the granular layer and before the formation of the supra-granular pyramids (*Mott*).

(3) The supra-granular pyramids—as already was proved by Dr. Mott are the latest to appear—have chiefly associative functions of a higher order,\* and, therefore, are just as much dependent on the surrounding regions as on the region where they are found. This can be proved phylogenetically and also pathologically, as they remain very much the same after localised sub-cortical lesions.

(4) The first tactile neo-cortical centre (occurring in Reptiles) belongs to the trigeminal sensibility. This has to be explained by the associative functions between olfactorium and oral sensibility.

(5) The neo-cortex originates from the palæo-cortex, and not from the archi-cortex. This explains why the corpus callosum (commissure of the neo-cortex) in the lower mammals originally runs ventrally together with the anterior commissure (commissure of the palæo-cortex), and not dorsally with the psalterium (commissure of the archi-cortex).

\* See note under † on previous page.

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PLATE I.



FIG. 1.  
A part of the palæo-cortex of *Scyllium canicula*



FIG 2.  
Cells of the granular  
layer of the palæo-cortex  
of *Scyllium canicula*.



FIG. 3.  
Cells of the infragranular layer of the palæo-cortex  
of *Scyllium canicula*.





PLATE II.

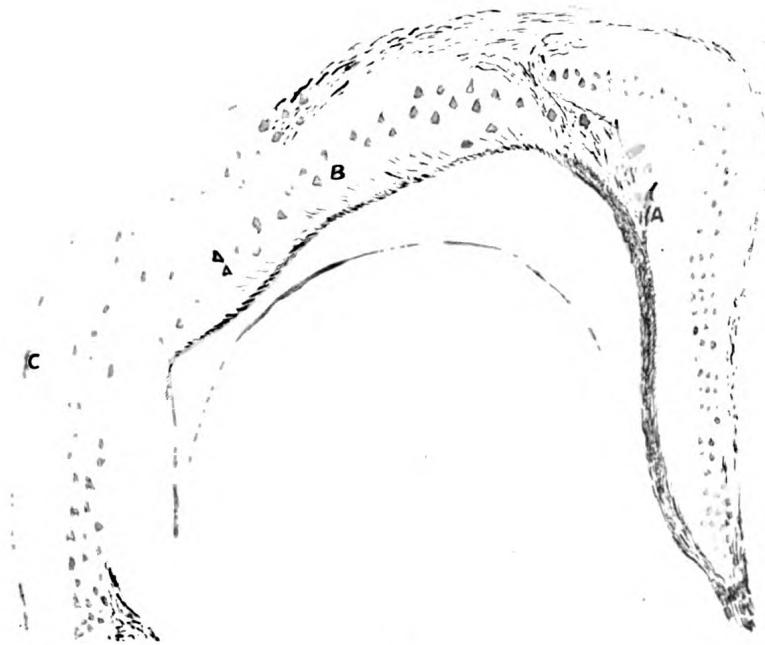


FIG. 4.

The pallium of *boa constrictor*.

A is the fascia dentata.  
B is the ammon formation.  
C is the lateral cortex, which originally represents the palæo-cortex, but here already includes the first rudiment of Neo-cortex, and dorsally a small associative group of cells.



FIG. 5.

Cells of the upper part of the lateral cortex of *boa constrictor*.

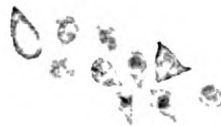


FIG. 6.

Cells of the fronto-basal part of the palæo-cortex of *boa constrictor*.



PLATE III.



FIG. 7.

Occipital pole of the brain of *Hypsiprymnus rufescens* (where the palaeo-cortex and archi-cortex meet).



FIG. 8.

Fronto-basal part of the palaeo-cortex of *Hypsiprymnus rufescens*.

FIG. 9.  
Granula-like cells in the fronto-basal part of the palaeo-cortex of *Hypsiprymnus rufescens*.



FIG. 10.

Pyramidal infragranular cells in the fronto-basal part of the palaeo-cortex of *Hypsiprymnus rufescens*.



PLATE IV.



FIG. 11.  
Granule cells in the fascia  
dentata of *boa constrictor*.



FIG. 12.  
Pyramidal cells in the ammon formation of *boa constrictor*.

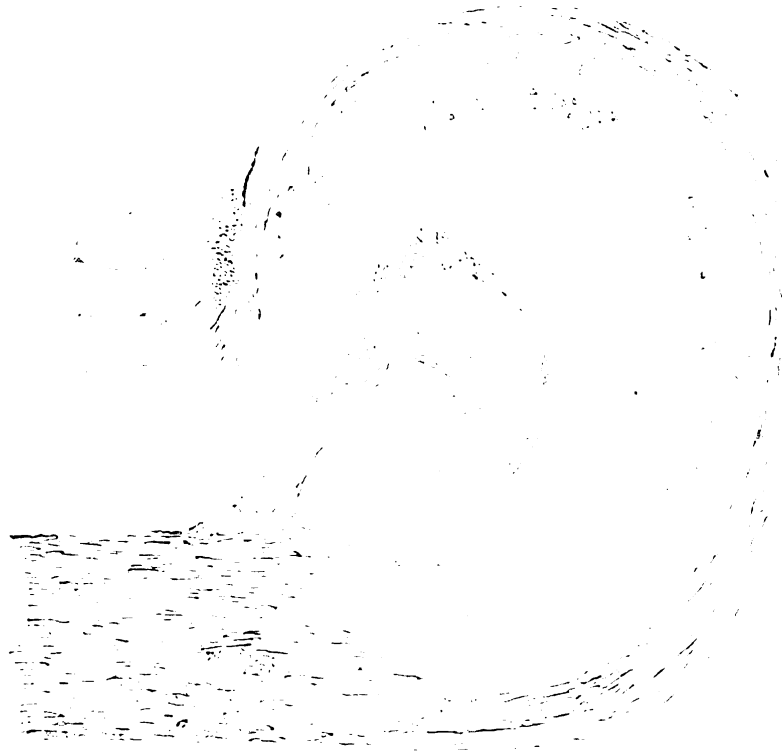


FIG. 13.—Archicortex of *Hypsiprymnus rufescens*.

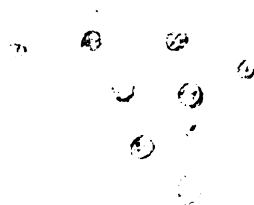


FIG. 14.—Pyramidal cells in the ammon formation of  
*Hypsiprymnus rufescens*.



FIG. 15.  
Granule cells in the fascia dentata  
of *Hypsiprymnus rufescens*.



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**A CHEMICAL STUDY OF THE BRAIN IN HEALTHY AND  
DISEASED CONDITIONS, WITH ESPECIAL REFERENCE  
TO DEMENTIA PRÆCOX.**

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Physiological Laboratory of the University of Chicago.*)

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## I.—INTRODUCTION.

At the suggestion of Dr. F. W. Mott, F.R.S., the methods for the chemical study of the brain outlined in a previous paper (1) by one of us (W. K.) have been extended to the study of certain mental disorders. In the course of the work the above methods have been frequently revised and elaborated, and we take this opportunity of republishing them in their amended form.

Attempts have been made by various observers to study the chemistry of mental disorders by analysis of the various bodily fluids and excretions, such as the blood, cerebrospinal fluid and urine. Results obtained by this method are difficult of interpretation and are liable to lead to erroneous conclusions. With regard to the examination of the urine, Folin and Schaffer (2), using carefully elaborated analytical methods, have completed an exhaustive work, and have come to the conclusion that there is little information to be obtained by attacking the problem solely through this source, and, further, that the large number of observations on record based on analysis of the urine and regarding the relation of an abnormal metabolism of the body to mental derangement, are of little value. The more recent observation of Pighini (*Vide* p. 220), that there is an increase of neutral sulphur in the urine in dementia præcox can be explained as being due to a general decrease in the oxidations and can be produced experimentally, as Richards and Wallace (3) have shown, by cyanide poisoning. This result, however, is of interest in view of the change in the neutral sulphur content of the brain (*Vide* p. 209) in this form of mental disorder.

The cerebrospinal fluid bears a more direct relationship to the nervous system and offers good opportunities for the chemical study of the products of nervous metabolism, but the amount of fluid which can be safely withdrawn by lumbar puncture during life is not sufficient to allow of accurate quantitative estimations. Qualitative tests, however, have shown in certain morbid conditions the presence of various products of degeneration, *e.g.*, choline (Mott and Halliburton (4)), and in general paralysis especially, a disease in which the fluid is in great excess, the protein and lipoid constituents are found to be increased in amount. In view of the significance which has been attached to the Wassermann Plaut reaction in cases of general paralysis and other parasymphilitic affections, the further study of the protein and lipoid constituents in the serum and cerebrospinal fluid of these cases is of great importance in deciding the chemical nature of the substance causing the complement deviation.

*Examination of the nerve tissue—(a) Micro-chemical.*—By far the

largest number of investigations of the nervous system itself have been concerned with such histological methods of staining as devised by Weigert, Nissl, Golgi, Ramon y Cajal, Held, and others. These investigations have shed light on the anatomical structure of the brain, but on account of our great lack of knowledge of the chemical constituents of the nervous system which are involved in these reactions, comparatively few have been regarded in the light of micro-chemical reactions. Gustav Mann (5), in his excellent text-book of physiological histology has stated practically all that can be said on the subject. Micro-chemical methods may decide points of anatomical distribution of constituents in a qualitative manner and correlated with quantitative macro-chemical observations lead to important conclusions. Thus in two cases of amaurotic dementia Mott (6) was able to associate the disappearance of the Nissl substance in the neurons with a decrease in nucleo-proteid, and an increase of the glia fibrils with an increase of simple proteid, the brain in each case being chemically examined by one of us (S. A. M.).

*Examination of the nervous system*—(b) *Macro-chemical*.—The study of the quantitative variations in the composition of the brain under normal and pathological conditions has so far received but little attention. In fact, this may be said of any tissue of the body on account of our lack of knowledge of the substances to be estimated. Our present knowledge permits us only to refer to groups of substances which in the nervous system may be arranged under the following general headings:—

1. Lipoids.—Phosphatids, cerebrins, cholesterin, and a sulphur compound.
2. Extractives.—Organic water soluble compounds not colloidal in nature, *e.g.*, kreatin, taurin, hypoxanthin, etc.
3. Inorganic constituents.—Ash.
4. Proteins.—Nucleoproteins, globulins, neurokeratin.

A more detailed account of the chemical constituents isolated from the brain was given in the 1904 paper, and for the sake of completeness it is here brought up to date.

#### CHEMICAL CONSTITUENTS OF BRAIN TISSUE.

1. WATER.— $H_2O$ , present in largest amount.
2. SIMPLE AND COMPOUND PROTEINS (C, H, O, N, S, P).  
*Globulin* coagulating at  $47^{\circ}$ – $50^{\circ}$  C. (Halliburton (7)).  
*Globulin* coagulating at  $70^{\circ}$  C. (Halliburton (7)).  
*Neurostromin* (Schkarin (8)).—Extracted by sodium hydrate, present only in small amount.

*Nucleoprotein* (Levene (9)).—Contains 0.57 per cent. phosphorus. The nuclealbumin of Halliburton (7) and the neuroglobulin of Schkarin (8) may be considered to be identical or closely related to the compound isolated by Levene.

*Neurokeratin* (Kühne and Chittenden (10)).—An albuminoid insoluble in sodium hydrate and not digested by ferments.

3. EXTRACTIVES (water soluble) (C, H, O, N, P, S).

*Hypoxanthin*.— $C_5H_4N_4O$  (Thudichum (11), p. 319).

*Tyrosin*.— $C_9H_{11}NO_3$  (trace) (Thudichum (11), p. 330).

*Leucin*.— $C_6H_{13}NO_2$  (trace) (Thudichum (11), p. 332). Both evidently derived from *post-mortem* decomposition.

*Urea*.— $CH_4N_2O$  (Gulewitsch (12)): its presence is not due to contamination with blood (essential constituent).

*Peptones and albumoses*.—(Thudichum (11), pp. 316-317) considers the osmazon of the French chemists to be closely related to this group.

*Sarcolactic acid* (Thudichum (11), p. 317).

*Formic, acetic, succinic, and lactic acids* (Thudichum (11), p. 329).—May be considered to be derived from *post-mortem* decomposition.

*Inosit*.— $C_6H_{12}O_6 \cdot 2H_2O$  (Thudichum (11), p. 319). The presence of this substance has been confirmed by a number of investigators.

*Taurin* or some immediate antecedent (Koch (13)).

*Kreatin*.— $C_4H_9N_3O_2$  found to be present by the method of Grindley (28).

Besides the above-mentioned substances, the following have been occasionally found to be present under pathological conditions by various authors, and must be considered on account of introducing sources of error in the methods of determination, especially with pathological material; they are: Neuridin (Brieger (14)), uric acid (Thudichum (11), p. 318); choline (Mott and Halliburton (5)) also, according to Gulewitsch (12), present as a normal constituent; trimethylamine (Thudichum (11), p. 330), evidently the result of *post-mortem* change.

#### 4. INORGANIC CONSTITUENTS.

Na, K,  $NH_4$ , Ca, Mg, Fe, present partly as dissociated ions, and partly in organic combination.

#### 5. PHOSPHATIDS (C, H, O, N, P).

*Lecithins*.—Stearyllecithin,  $C_{44}H_{86}NPO_8 \cdot OH$ ,

Margerylecithin,  $C_{43}H_{84}NPO_8 \cdot OH$ ,

Palmitylecithin,  $C_{42}H_{82}NPO_8 \cdot OH$ ,

isolated as a mixture of isomers and homologues by Thudichum (11, pp. 322, 123) and Koch (15), are all characterised by the presence of three methyl groups attached to nitrogen. One methyl group splits off quan-

titatively at 240° C. with hydriodic acid, the remaining split off at 300° C. These lecithins have basic properties, form double salts with cadmium chloride, but do not form insoluble lead salts. They are soluble in alcohol and ether. Phosphorus, 4 per cent.; nitrogen, 1·8 per cent. Proportion 1:1.

*Amidolecithins*.—Amidomyelin,  $C_{44}H_{88}N_2PO_8$ . Isolated so far only by Thudichum (11, pp. 322, 123, 110), who has not published complete analyses. From the empirical formula, this substance evidently is closely allied to the lecithins, and should have three methyls attached to nitrogen. The quantitative results indicate that this substance can be present only in extremely small amount. Nitrogen, 3·5 per cent.; phosphorus to nitrogen as 1:2.

*Kephalins*:—

Kephalin,  $C_{42}H_{79}NPO_{13}$  (Thudichum (11), pp. 320, 130; Koch (15)).

Oxykepbalin,  $C_{42}H_{79}NPO_{14}$  (Thudichum (11), p. 138).

Peroxykepbalin,  $C_{42}H_{79}NPO_{15}$  (Thudichum (11), p. 138).

Myelin,  $C_{40}H_{75}NPO_{10}$  (Thudichum (11), pp. 323, 156).

These substances are derived from the lecithins by the loss of two methyl groups and an oxidation of the oleic acid radicle, the chemistry of which is very obscure. In consequence of the nitrogen becoming a triad, the basic properties are lost, and these substances consequently give insoluble lead salts. The methyl group is split off quantitatively at 240° C. with hydriodic acid. No more methyl is split off above that temperature. A comparison of the formula makes it evident that kepbalin  $C_{42}$ ..... is derived from stearyloley l lecithin  $C_{44}$ ..... and myelin  $C_{40}$ ..... from palmityloley l lecithin  $C_{42}$ ..... These substances are soluble in ether, insoluble in alcohol. Phosphorus, 3·7 per cent.; nitrogen, 1·7 per cent. Proportion of 1:1.

*Amidokephalins*.—Amidokephalin,  $C_{42}H_{80}N_2PO_{13}$ . Isolated so far only by Thudichum (11, p. 107), may be considered to be derived from the amidomyelin by the loss of two methyl groups and an oxidation similar to kepbalin. The empirical formulæ support this theory. Phosphorus to nitrogen as 1:2.

Besides the above-mentioned, the following compounds, which are difficult to classify, have been isolated by Thudichum:—*Paramyelin*,  $C_{38}H_{75}NPO_9$ , probably related to lecithin. *Sphinaomyelin*,  $C_{52}H_{104}N_2PO_9$ , recently confirmed by Rosenheim (39), probably related to the amidolecithins (nitrogen 3 per cent.), containing however, no glycerine. *Assurin*,  $C_{16}H_{94}P_2O_9$ . (Phosphorus 7 per cent.; nitrogen 3·2 per cent.).

6. CEREBRINS (C, H, O, N).

Within recent years these substances have been studied on human

material by Thudichum (11, p. 178) and Thierfelder (16), on sheep's brains by Koch (15), and on horses' brains by Bethe (17, p. 78), and more recently confirmed by Rosenheim. As there is very little difference in the cerebrins derived from different species it will simplify matters to compare them regardless of their source.

*Phrenosin*,  $C_{41}H_{79}NO_8$ . The substance isolated by Thudichum (11, p. 184) may be said to be identical or isomeric with that isolated by Thierfelder and by Koch, as will be seen from a comparison of the analyses:—

	THUDICHUM.	THIERFELDER	KOCH.
Carbon ...	69.00	69.16	68.73
Hydrogen ...	11.08	11.54	11.83
Nitrogen ...	1.96	1.76	1.64

Phrenosin spits off galactose on heating with dilute mineral acids.

*Kerasin*,  $C_{44}H_{88}NO_8$  (Thudichum (11), p. 218), probably identical with Bethe's (17, p. 184) *amidocerebrin acid glycosid*,  $C_{44}H_{81}NO_8$ . Both are undoubtedly homologues of phrenosin, and in the same way split off galactose.

*Phrenin*, isolated by Bethe (17, p. 184), was obtained by Koch as a decomposition product from cerebrin after boiling with dilute hydrochloric acid. The analyses agree fairly well.

	BETHE.	KOCH.
Carbon ...	71.90	71.60
Hydrogen ...	11.95	12.14
Nitrogen ...	1.5	1.89

This substance does not split off a reducing sugar as do phrenosin and kerasin.

*Cerebrin acids* so far only isolated by Thudichum (11, p. 221).

*Cerebrin acid*,  $C_{49}H_{99}NO_{11}$ , and *sphaerocerebrin*,  $C_{58}H_{123}NO_{17}$ , are characterised by forming lead salts insoluble in hot alcohol. This distinguishes them from kerasin and phrenosin, which do not combine with lead. Cerebrin acid, according to Thudichum, splits off galactose. A comparison of the percentage of carbon found by Thudichum makes it extremely probable that these substances are intermediary oxidation products of phrenosin and kerasin, as indicated by the following figures:—

	PHRENOSIN.	CEREBRIN ACID.	SPHAEROCEREBRIN.
Carbon ...	69.0	67.00	62.75
Hydrogen ...	11.08	11.36	11.08
Nitrogen ...	1.96	1.59	1.23

No other substances have been isolated which may be said to belong to the group of the cerebrins. The cerebrinphosphoric acid of Bethe is

only an impure mixture which undoubtedly contains sulphur, for which he neglected to test. None of the members of this group can be said to be pure until they are free from sulphur and phosphorus, both of which elements cling to them most tenaciously. All the cerebrins when pure are insoluble in ether and soluble in hot alcohol. The cerebrin acids are more soluble in glacial acetic acid than phrenosin.

7. CHOLESTERIN (C, O, H),  $C_{27}H_{45}OH$ , occurs in the brain as free cholesterin and not in the form of esters. Soluble in hot alcohol and cold ether. Bünz (18). Tebb (19).

8. SULPHUR COMPOUNDS (C, H, O, N, P, S).—Thudichum (11, p. 224), Koch (13).

9. AMIDOFATS (C, H, N, O).

*Krinosin*,  $C_{38}H_{79}NO_5$ .

*Bregenin*,  $C_{40}H_{81}NO_5$ .

These substances have so far been only isolated by Thudichum (11, p. 227). They are distinguished from fats by their insolubility in ether. The quantitative determinations indicate that they may be present in small amount only. They most probably represent *post-mortem* decomposition products.

10. MONOPHOSPHATIDS (C, H, O, P).

*Lipophosphoric acid*, *butophosphoric acid*.—Isolated by Thudichum (11, p. 177), but not analysed completely. Contain about 4 per cent. of phosphorus, and are free from nitrogen. May be present in slight amount in white matter, as not quite all the phosphorus is accounted for. Most probably, however, they are either *post-mortem* decomposition products or the result of chemical manipulation.

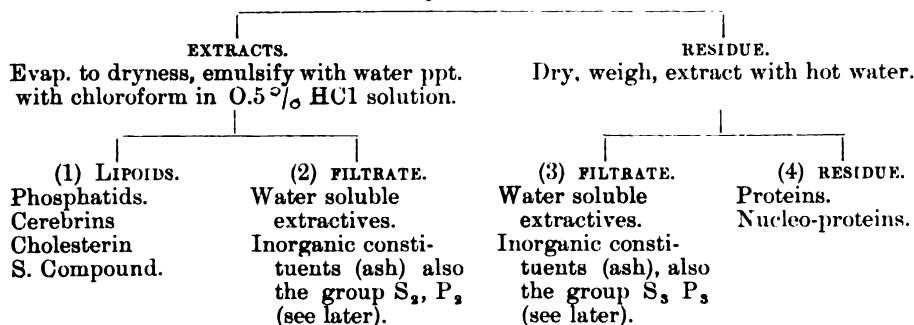
This completes the list of substances isolated or supposed to have been isolated from brain tissues. Free fats and fatty acids have never been found to be present in normal brain tissue. Bethe (17, p. 86) mentions stearic acid but adds a question mark, which is a wise provision, as he has been rather unfortunate in describing decomposition products as primary constituents (phrenin, *see above*). Protagon we have no intention in resurrecting, in spite of fears to the contrary (20), as the work of Thierfelder (16), Gies (21), and Rosenheim and Tebb (22) has settled its fate. For further discussion on this subject, *see also* Cramer (23, 24).

*Principles of estimation of constituents*.—These constituents are separated into the four general groups mentioned above (p. 176) by solvents according to the following outline: Alcohol has proved to be the most satisfactory solvent, and, although it is desirable in a quantitative study of this kind to rely on methods of separation by solvents as little as possible, observations which are recorded later

(p. 188), indicate that the separation of lipoids from the proteins is as good as can be found at present.

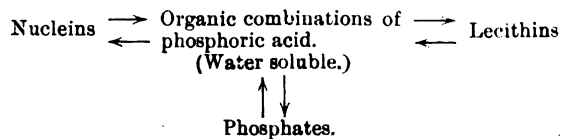
#### MOIST TISSUE.

Add alcohol and extract alternately with alcohol and ether.



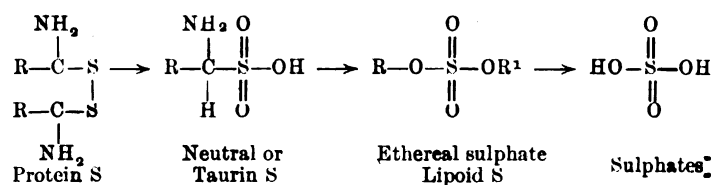
Besides studying the variations of the constituents as cerebrin, protein, which may be looked upon as the *food* supply of the brain, in normal and pathological cases, the variations of the distribution of the elements phosphorus and sulphur among the various groups were also investigated. The selection of these two elements was based on the following considerations.

*Phosphorus* occurs in the body exclusively as combinations of phosphoric acid, an oxidised derivative. Its mechanism of absorption and intermediary metabolism is not yet fully understood, but it is quite certain that it enters the system either as a phosphate or some simple organic derivative and leaves in the form of an acid phosphate. It is the radicle which seems to play the rôle in the building up of the most complex constituents of the cell, the nucleins and phosphatids. The variation in its distribution between these and the water soluble extractives should therefore give an indication of the amount of destruction of these important cell constituents. The following outline will serve to make this clear:—



A relative increase of the water soluble phosphoric acid derivatives may be interpreted as being due to an excessive breakdown of nucleins and lecithins, or may occur during a condition of rapid growth where the food materials are supplied in abundance (25). During a condition of starvation, where, however, the reparative reaction is still going on, phosphates should be decreased (26).

*Sulphur* occurs in the body in various stages of oxidation. As —SH or cystin sulphur in proteins, as sulphonate or  $\text{R}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}\text{S}-\text{OH}$  or taurin like sulphur, and as ethereal and inorganic sulphates. Sulphur probably enters the organism largely as unoxidised or cystin sulphur and leaves to the extent of 95 per cent. in an oxidised form as inorganic sulphates. It differs, therefore, from phosphorus in undergoing a change in its state of oxidation as a result of the intermediary metabolism. It seemed possible, therefore, to utilise the variation in the different stages of oxidation of sulphur for measuring the extent to which oxidising reactions are going on in the tissues, especially as the work of Heffner (27) shows that the affinity of the sulphur group for oxygen plays a very important rôle in the organism. The relations are made plain by the following scheme:—



## II.—EXPERIMENTAL PART.

*Methods.*—Before entering into the details of the methods adopted, we consider that it will save the reader much confusion if we state in full the symbols by which we have designated the various sulphur and phosphorus fractions. Incidentally, we put this forward as a system of labelling, for it must be remembered that the examination of one brain lasts nearly one month, also the various fractions are constantly being transferred from one vessel to another, and when a few brains are being examined at the same time, a definite system of labelling must be adhered to.

The general scheme of separation then leads to four fractions:—

1. Alcohol soluble, insoluble in acid chloroform water (lipoids).
2. Alcohol soluble, soluble in acid chloroform water (extractives).
3. Alcohol insoluble, water soluble (extractives).
4. Alcohol insoluble, water insoluble (proteins).

It is in these various fractions that it is proposed to study the distri-



butions of the elements sulphur and phosphorus. These various fractions may then be designated :—

S<sub>1</sub>. Alcohol soluble, acid chloroform water insoluble, lipoid sulphur.

S<sub>2</sub>. Alcohol soluble, acid chloroform water soluble, extractive sulphur.

S<sub>3</sub>. Alcohol insoluble, water soluble, extractive sulphur.

S<sub>4</sub>. Alcohol insoluble, water insoluble, protein sulphur.

S<sub>2</sub><sup>I</sup> and S<sub>3</sub><sup>I</sup> represent inorganic sulphates, derived from these fractions by direct treatment with barium chloride.

The same applies to the phosphorus fractions.

P<sub>1</sub>. Alcohol soluble, acid chloroform water insoluble, lipoid phosphorus.

P<sub>2</sub>. Alcohol soluble, acid chloroform water soluble, extractive phosphorus.

P<sub>3</sub>. Alcohol insoluble, water soluble, extractive phosphorus.

P<sub>4</sub>. Alcohol insoluble, water insoluble, protein phosphorus.

P<sub>2</sub><sup>I</sup> and P<sub>3</sub><sup>I</sup> represent inorganic phosphates derived from these fractions by direct precipitation with magnesia mixture.

P<sub>1</sub><sup>L</sup> and P<sub>1</sub><sup>K</sup> represent lecithin and kephalin phosphorus as separated by the lead kephalin salt.

Such a system of notation is of great value in a large number of analyses. By adding the case number it is possible to tell after several months just how the material has been handled. Thus 23 P<sub>1</sub><sup>L</sup> × 5 refers to sample 23 and means the lecithin fraction of the total lipoid phosphorus multiplied by 5 on account of the fact that an aliquot part was taken. 70 S<sub>3</sub><sup>I</sup> means that in sample 70 the hot-water extract of the alcohol insoluble residue was precipitated direct with barium chloride in hydrochloric acid solution.

#### COLLECTION AND PRESERVATION OF MATERIAL.

The previous method of collecting the material by separation of the grey and white matter was only followed in a few cases, which will be given later. It soon became evident that, especially in the case of the grey matter, too much time would be required to collect the amount of material necessary to ensure accurate analyses in some of the sulphur and phosphorus fractions. As changes in the metabolism of the nervous system such as we are here seeking to investigate are more apt to affect the brain as a whole, it seemed advisable to take larger samples, and one half of the brain was used for chemical work and the other retained for histological examination.

The half of the brain intended for chemical work can be used either as a whole or for the separation of the cortex and corpus callosum. The membranes are removed and any blood washed away, and the brain

allowed to drain. This procedure vitiates any absolute estimation of the amount of moisture, but as this figure was never used except to refer the constituents to the per cent. of total solids, there is no error involved.

(a) *Collection of white matter from corpus callosum and adjacent centrum ovale.*—As much as possible of the corpus callosum and centrum ovale is dissected and all adhering particles of grey matter removed. It is then finely minced with scalpels and a two-gramme sample taken for the moisture determination. The remainder (50 grammes) is transferred to a 250 c.c. bottle and weighed. Absolute alcohol is added to nearly fill the bottle and the whole is well shaken. The following day the bottle is again shaken, heated to 75° C. by immersion in water at that temperature, and set aside for future analysis.

(b) *Collection of grey matter from cortex.*—The frontal and motor regions are utilised and the grey matter is trimmed off with a sharp scalpel without any adhering white matter. About 50 grammes of cortex is collected in this manner, minced, and mixed as well as possible, two grammes taken for the water estimation, and the remainder weighed and preserved the same as the corpus callosum. This mode of collecting the grey matter takes a considerable time, and requires much care and patience.

(c) *Collection of mixture of grey and white matter from the whole hemisphere.*—The whole of one hemisphere is passed through a mincing machine with a fairly fine wire mesh ( $\frac{1}{8}$ -inch), well mixed and again passed through the mincing machine, and three one-hundred-gramme samples taken. A sample this size ensures a sufficiently uniform mixture of the white and grey matter (*vide* p. 200), and gives amounts of barium sulphate and magnesium pyrophosphate in the various sulphur and phosphorus fractions large enough to give accurate weighings, and does not involve the extraction and destruction of inconveniently large amounts of organic material. The three 100-gramme samples are preserved in at least 400 c.c. of absolute alcohol each; allowing for the amount of moisture in the sample, this ensures a concentration of about 83 per cent. alcohol in the preserving fluid.

As some of the samples were analysed at different periods of time after the collection of the material, it seems of interest to compare them from the point of view of this method of preservation:—

Time between collection and analysis of sample ...	3 hours	2 days	2 weeks	3 months
Sulphur in alcohol soluble fraction ...	42.7	38.4	36.9	35.9
Sulphur in alcohol insoluble fraction ...	57.3	61.7	63.1	64.1
Phosphorus in alcohol soluble fraction ...	86.3	87.5	84.7	83.8
Phosphorus in alcohol insoluble fraction ...	13.8	12.5	15.3	16.3

The changes to be observed in the sulphur are evidently not due to lack of preservation, but indicate rather an incomplete coagulation of the proteins. After two or three weeks this coagulation seems to be complete, and the results then are more uniform. It is well, however, on the day after collecting the sample to thoroughly shake up the mixture so as to ensure complete penetration of the alcohol into the tissue, and to heat it up to a temperature just below the boiling point of alcohol by placing the bottle containing the sample in a water bath at 75° C.

One other factor needs to be considered in the collection of the material, *i.e.*, the amount of variation introduced by the time the material is kept after death before preservation in alcohol. It is quite impossible to avoid the immediate *post-mortem* changes which occur at the moment of cell death or possibly just before; but as the hospital and asylum brains were handled in much the same way this variation becomes constant. The differences between a brain collected one hour or thirty hours after death, however, need to be considered. As the differences are apt to take the form of autolysis or breaking up of the complex colloidal molecules into simpler ones they would influence the relation of the different fractions. The best means of measuring these would be by a study of the changes in the nitrogen, such as have been done frequently in studies of autolysis. As the nitrogen, however, has not been considered in these analyses, a comparison of the extractive or water soluble phosphorus will serve the purpose:—

Time of collecting after death.	Water soluble extractive P.	Lipoid and Protein P.
1 hour	26.9	73.0
4 hours	24.7	75.2
17 hours	24.7	75.3
19 hours	23.2	76.7
30 hours (cold chamber)	25.1	75.0

The results, if anything, show a change contrary to what might be expected if autolysis were proceeding, and, in view of the fact that these analyses were made on different samples, the variations are of little significance. The results are in harmony with other observations which indicate a very slow rate of autolysis in the brain. Nevertheless, the material should be collected within 24 hours after death if possible.

#### METHOD OF EXTRACTION—OUTLINE OF METHOD.

In the plan previously outlined (p. 181) for the separation of the different groups of constituents the following fractions are first obtained:—

- 1 and 2. Fraction soluble in alcohol (85-95 per cent.).
3. Fraction insoluble in alcohol, soluble in hot water.
4. Fraction insoluble in alcohol and hot water.

Although ether is used in the extraction following the first alcohol, it does not remove any considerable amount of material and need not be considered in the above scheme. The apparatus used for the extractions is a modification of the old form of Wiley extraction apparatus, and was designed for us, according to our suggestions, by Gallenkamp and Co., London. The advantage of this form over the Soxhlet, especially for work with nerve tissues, consists in the fact that the extraction takes place at the boiling point of the solvent.

The apparatus (Fig. I.) consists of a wide mouth  $\text{CO}_2$  flask of 300 c.c. capacity into which it is fitted, by means of a ground glass connection, a small double surface condenser. On the lower end of the condenser are

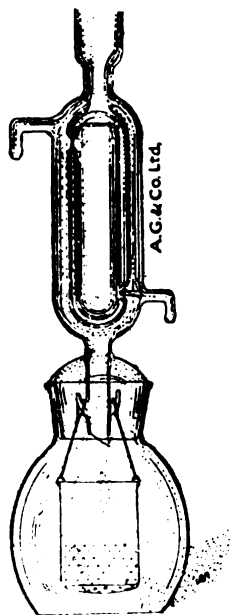


FIG. I.

fused two glass hooks, from which is suspended in a thin platinum wire sling a 40 c.c. perforated cup. Each condenser is fitted with at least three interchangeable flasks. If dry heat is used for the extraction (cf. Electric Plate, Plate I.) the above form of condenser answers admirably, but should a water bath be used, the escaping steam will condense on the external surface of the condenser and, creeping into the ground glass connection, will possibly cause it to stick. With a water bath, a Hopkin's condenser (Fig. II.)—in which the cooling is accomplished from the inside—prevents this source of annoyance. Electric hot plates have the disadvantage that they are heated irregularly, but we have found

PLATE I.





them, *used carefully*, to effect a great saving in time, and also to eliminate all risk of fire. Plate I. shows a number of extractions proceeding at the same time; these, when once started, require but little supervision, and can be left running during the night for the final extractions.

For the extraction the material is transferred to the perforated cups and first extracted for 3-4 hours with 95 per cent. alcohol. As this removes about nine-tenths of the alcohol soluble portion, it is better to discontinue heating on account of the danger of decomposing some of the compounds now in the alcohol solution. The alcohol extraction is

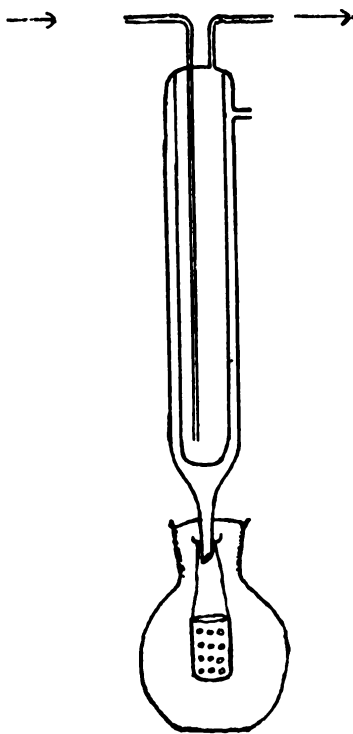


Fig. II.

followed with an ether extraction, and this, although it does not remove much material, has the advantage of rendering the nerve tissue extremely brittle, so that it can be finely powdered, which procedure greatly aids the completeness of the later extraction. After powdering, the material is mixed with water and heated; absolute alcohol is then added to bring the concentration to at least 85 per cent. This procedure ensures the more complete extraction of those extractives, which are only slowly soluble in 95 per cent. alcohol, but which, if the extraction were continued long enough, would finally come out and really belong to the alcohol soluble

fraction. The material is again transferred to the cups and extracted for twelve hours with 95 per cent. alcohol. To continue the extractions longer than this is hardly necessary, for, although it is practically impossible to separate completely the constituents of any tissue by extraction with solvents, the following control experiment indicates that the error is not very great.

One hundred grammes of brain material were extracted twice with alcohol and once with ether, as outlined above and described in detail later, and the amounts of sulphur and phosphorus removed estimated. The material was then again ground up and remixed and subjected to another alcohol extraction for twelve hours, and the total sulphur and phosphorus in the extract estimated. The results are as follows:—

4 hours alcohol, 2 hours ether, 12 hours alcohol extractions yielded	...	...	...	...	...	253.7 mg. BaSO <sub>4</sub>
A further 12 hours alcohol extraction yielded...	...	...	...	...	...	6.5 mg.
						<hr/> 260.2
Percentage extracted in first series	...	...	...	...	...	97.5

On the same sample phosphorus estimations were made and yielded:—

First fractions	...	...	...	...	...	893.1 mg. Mg <sub>3</sub> P <sub>2</sub> O <sub>7</sub>
Final fraction	...	...	...	...	...	6.0 " "
						<hr/> 899.1 " "
Percentage extracted in first series	...	...	...	...	...	99.3

Although the total amount of sulphur extracted in the final fraction is only 0.9 mg. as compared with 1.7 mg. phosphorus, it calculates to a little higher in percentage of total on account of the smaller amount of total sulphur extracted with alcohol. The completeness of the extraction is, therefore, fairly satisfactory, especially as the error largely becomes eliminated in a series of comparative experiments such as we are dealing with here.

The residue insoluble in alcohol represents essentially proteins (the amount of glycogen in nerve tissue is too small to be considered) plus a correction for water soluble alcohol insoluble extractives (about 2 per cent. of the total residue). As these extractives, however, are rich in inorganic phosphates and sulphates, it is necessary, after weighing, to extract this residue with hot water. Eight extractions are usually sufficient. In these extractions it is well to exercise great care to avoid the danger of bacterial decomposition, as the results can be completely vitiated by this source of error.



## DETAILS OF METHOD.

One hundred grammes of brain material which have been preserved in 400 c.c. of absolute alcohol and kept with occasional heating to ensure complete coagulation of the proteins for not less than two or more than four months, are transferred to the cups as follows:—The perforations of three cups are covered with filter paper by cutting one round piece to fit the bottom end and one oblong piece to fold against the side. The filter paper is moistened with alcohol and pressed firmly against the sides with a glass rod. Even if all the perforations are covered with filter paper, small particles of brain material will pass through the cracks where the two pieces join, but if the adjustment of the filter paper has been carefully done, these cracks soon fill up and the filtrate is perfectly clear. The cups are then placed in large funnels which drain into beakers placed below and the brain material carefully transferred. It requires three cups to hold 100 grammes of brain material.

At first, as stated above, the filtrate is not clear, but when it begins to come through clear the beakers are changed and the first filtrate refiltered. After all the material has been transferred to the cups in this manner and the last particles washed in with hot alcohol, the cups are allowed to drain and then carefully transferred to the extraction apparatus.

In order to ensure a better distribution of the alcohol, as it drips into the cup from the condenser, a perforated plate is placed on top of the brain material in the cup; the extraction is started with 95 per cent. alcohol at the medium temperature of the electric plate and continued for 3–4 hours. With this temperature the alcohol boils, and about every two seconds one drop falls from the condenser and thus keeps the material thoroughly soaked. After 3–4 hours the apparatus is allowed to cool, clean flasks substituted, and an ether extraction continued for 2–3 hours. The apparatus is again allowed to cool and the material carefully ground up to as fine a powder as possible in an agate mortar. When removing the material from the cups, care must be taken not to disturb the filter paper, as it is to be used again when the material is returned to the cups. The powdering of the material may be a slow and laborious process, but should be carefully and completely done in order to ensure complete extraction later. The powdered material is transferred to a 600 c.c. Jena flask, moistened with 50 c.c. water and heated on a water bath for one hour. At the end of this time 450 c.c. absolute alcohol are added; the mixture is warmed, well shaken and allowed to stand over-night. The material is again filtered into the cups, as previously described, and extracted for twelve hours with 95 per cent. alcohol. The flasks contain-

ing the alcoholic extracts, the beakers containing the filtrates, and the flasks containing the ether extract are put aside, and their manipulation will be described later under the separation of the lipoids. The residue in the cups is now transferred to a weighed beaker or platinum basin and dried at  $105^{\circ}$ – $110^{\circ}$  C. to constant weight. This weight represents the total protein plus about 2 per cent. of extractives and ash (not removed by the alcohol), and is designated as fraction 3 and 4. It is now necessary to take an aliquot part for the  $S_{3+4}$  estimation. In the dry and very hygroscopic condition of the protein residue this is practically impossible; therefore, after weighing, it is allowed to stand over-night in order to come back into equilibrium with the moisture of the air, it is then again weighed and an aliquot part of one gramme taken for the  $S_{3+4}$  estimation (p. 196). The remainder is transferred to a 300 c.c. Jena flask and moistened with 100 c.c. water; the flask is plugged with a loose cotton wool stopper and heated on a water bath for one hour. This eliminates all risk of bacterial decomposition until next day, when the fluid is filtered into a 600 c.c. Jena beaker. The residue is washed back into the flask and 100 c.c. water again added and the process repeated on each of eight successive days. It is imperative that after the cotton wool stopper has been removed, the material is not kept too long before it is again sterilised. The precautions are merely those which will occur to anyone familiar with bacteriological technique. One point, however, may escape notice. In case it is not possible on account of press of work to start the water extractions the next day after the residue has been dried, it is not safe to allow it to stand. The amount of moisture which is absorbed from the air is sufficient to enable bacteriological growth to commence, and we have frequently noticed samples which, although they were dry when transferred to a dry flask, develop a decided odour of putrefaction on standing. It is advisable in such a case to thoroughly soak the residue in 15–20 c.c. chloroform and carefully stopper it before putting it aside.

The filtrates from the hot-water extractions, as they stand for more than a week before the process is ended, are also liable to bacterial decomposition. The addition of 5 c.c. of conc. hydrochloric acid to the first filtrate avoids this difficulty. When the filtrates accumulate to more than 400 c.c., they must be evaporated so as to keep the bulk at about 300 c.c. The precipitate at first formed when the acid is added to the first filtrate is practically redissolved by this process. A slight amount of a brownish precipitate sometimes forms in the solution, and should be filtered out before the  $S_3^1$  estimation is made, but not before the total  $S_3$  estimation, as it may contain traces of organic sulphur compounds. The united filtrates, which should not exceed 300 c.c. in

bulk, are then used for the  $S_3^I$  or  $S_3$  and  $P_3$  estimations (pp. 196 & 200). The residue insoluble in hot water is burned by Neumann's method with nitric and sulphuric acids, and used for the  $P_4$  determination (p. 200).

#### SEPARATION OF LIPOIDS.

The alcohol soluble portion (fraction 1 and 2 of the 100 gramme of brain matter) is now contained in three flasks from the first alcohol extraction, three flasks from the ether extraction, two flasks from the second alcohol extraction, and five beakers, three from the first filtrate in which the sample was originally preserved, and two from the treatment after grinding the material in agate mortar. In the first set of these flasks a considerable amount has separated on cooling. The supernatant liquid is carefully decanted off into several 250 c.c. Jena glass evaporating dishes, into which all the other extracts are poured as the evaporation proceeds. The evaporation must be carried on at a low temperature, and in no case must the samples be evaporated to dryness. After they have been reduced to small volume, the residual liquids are allowed to cool and the evaporation finished in a vacuum desiccator. All the alcohol must be removed as completely as possible, as it interferes with the later procedure. After about one week the samples are dry and free from alcohol. They are then moistened with water, allowed to stand over night and the next day transferred to a graduated 1,000 c.c. flask. If the material has been well moistened it can easily be removed from the beakers and extraction flasks as a watery emulsion. After all has been transferred to the litre flask it is well shaken and 10 c.c. conc. hydrochloric acid added. After again shaking 15 c.c. chloroform are added and the bulk made up to 1,000 c.c., well shaken and allowed to stand in a cool place for three to seven days, when a perfectly clear filtrate can be obtained. The danger of decomposition of the lipoids from this acid treatment has already been investigated (1) and occasional control experiments made in the course of the work have confirmed these negative results. If the filtrate is not perfectly clear, it can be shaken up again with chloroform and allowed to stand in a cool place; the solution is then again filtered through a fresh filter paper. In order to obtain a complete separation of the lipoids and the water soluble extractives it would be necessary to wash the lipid precipitate with acid water. This, however, has not been found practicable, but instead the filter paper containing the lipid precipitate is allowed to drain thoroughly and the volume of the filtrate recorded. The difference between this volume and the total volume minus the chloroform approximately represents the amount of liquid adhering to the lipid precipitate. In order to make this figure more

accurate it is necessary to start the filtration through a dry filter paper. The following example will illustrate the case (compare also similar case, p. 197):—

The residue from the evaporation of the total alcoholic extracts of 100 gms. of brain matter were emulsified with water and 10 c.c. HCl and 15 c.c.  $\text{CHCl}_3$  added. The whole was made up to 1,000 c.c., well shaken and allowed to stand five days. The filtrate measured 780 c.c., and yielded on evaporation by the method of sulphur estimation (p. 195) 69·7 mg.  $\text{BaSO}_4$ . The lipid precipitate collected from the filter paper by dissolving in hot alcohol yielded 259·0 mg.  $\text{BaSO}_4$ . Considering that if all the filtrate adhering to the lipoids could have been recovered and allowing for the volume of chloroform, the part of the 205 c.c. difference must be due to the bulk of the lipoids, but if we consider that 100 grammes of brain matter contains only 22 grammes of solids, of which 60 per cent., or 13 grammes, is represented by lipoids, the error is not very considerable. Therefore, we have assumed that the 205 c.c. have the same composition as the other 780 c.c., and that, by calculation, they would yield 18·3 mg.  $\text{BaSO}_4$ , which must be subtracted from the lipid sulphur, leaving 240·7 mg.  $\text{BaSO}_4$ , total  $\text{S}_1$ , and added to the extractive sulphur, making 88·0 mg.  $\text{BaSO}_4$ —total  $\text{S}_2$ . The proportional error in this manner of correction is probably much less than would be incurred by attempting to wash the lipoids.

#### ESTIMATION OF SULPHUR.

##### *Outline of method:—*

In searching for a method suitable for the estimation of sulphur in the moist fatty material with which we are dealing, and in which it is sometimes necessary to estimate accurately 5-10 mg. of sulphur in 2-3 grammes of organic material, the following difficulties must be taken into account:—(a) The possibility of loss from too rapid combustion, especially with dry material, and the danger of spattering with material in a semi-liquid state. (b) The risk of incomplete combustion or oxidation, due to caking of the fusion mixture.

In an excellent review of all the methods Folin (29) finally recommends the sodium peroxide method. This, however, did not prove satisfactory with the moist fatty material we have been investigating, and the method used by Schmiedeberg in his laboratory has been adopted. This method gives very good results in cases where large amounts of organic material have to be destroyed, but it requires much time and care. The principle of the method consists in the gradual charring with an alcohol burner of the material in a mixture of seven

parts sodium carbonate and one part potassium nitrate. This proportion of potassium and sodium avoids the source of error, pointed out by Folin, in the precipitation of the barium sulphate. The final burning is made with a Barthel alcohol burner at a temperature just below the fusion point of the mixture. After acidifying with hydrochloric acid a few drops of bromine water are added to remove any nitrous oxide in the solution, and the precipitation is done in the usual way.

*Description of method*—(a) *Method of fusion*.—One gramme of the material is mixed with at least 12–15 grammes of the fusion mixture ( $\text{Na}_2\text{CO}_3$  seven parts,  $\text{KNO}_3$  one part) in a lipped silver crucible of 30 c.c. capacity, and *very gradually* charred over an alcohol spirit lamp. This process should take several hours, and the fumes from the burning should never rise so rapidly as to discolour very much the top layer of the fusion mixture. Should the fumes come off too rapidly, the spirit lamp must be removed for a short time and fresh fusion mixture sprinkled on the top of the mixture. In this manner the fumes arising from the burning are made to pass through a layer of fresh fusion mixture, and any sulphur fumes are kept back. After the material has completely charred and no more fumes come off even on placing the flame in direct contact with the crucible, the mass after cooling is thoroughly powdered in an agate mortar with the addition of about 1–2 grammes of fresh fusion mixture. It is then returned to the crucible, a layer of fusion mixture sprinkled on top, and heated with the Barthel alcohol burner at a temperature sufficiently low to avoid caking of the fusion mixture. The burning must not be hurried. The combustion will be more complete after heating at a moderately low temperature for half an hour, than by trying to force the process, for any caking is apt to include black specks which are difficult to oxidise, and not only may contain unoxidised sulphur, but also actually reduce some of the sulphates already formed, *e.g.*, the Leblanc soda ash process. The fusion mixture, after cooling, is transferred to a 600 c.c. Jena Erlenmeyer flask, and the crucible boiled out twice with hot water to dissolve any silver sulphate which may have formed through contact with the crucible. If the mixture has caked a little this process of boiling out becomes much more difficult, and almost invariably a black stain of silver sulphide will be seen on the crucible. The loss from this source of error may amount to 1 mg. of  $\text{BaSO}_4$ . The solution with washings is carefully acidified with hydrochloric acid and heated on a water bath to drive off the  $\text{CO}_2$  evolved. It is then filtered and to the boiling filtrate 5–10 c.c. of 10 per cent.  $\text{BaCl}_2$  solution are added and the barium sulphate estimated in the usual manner.

It is usually considered advisable in making sulphate estimations to obtain a weighing of 100 mg. or more of barium sulphate. As this would

involve the destruction of very large amounts of organic material it was decided in these analyses to aim at 40–60 mg. of barium sulphate, considering that the error occasioned by a somewhat smaller weighing would be more than compensated for by the more complete extraction of the material and the decrease in the sources of error accompanying the destruction of large amounts of organic material. The 100 grammes sample of moist brain material recommended in the collection of material accomplishes this.

*Estimation of  $S_1$ .*—The lipoids after filtration following the acid chloroform precipitation, represent a sticky mass adhering to the flask and filter paper. The mass on the filter paper can be washed off with hot alcohol. The destruction of all the lipoids from a 100-gramme sample, however, involves an almost hopeless task, and would yield about 250 mg. barium sulphate. In order to keep the estimation within the limits of accuracy, adopted for the other fractions, it becomes necessary, therefore, to take an aliquot part. This can only be done by dissolving the mass in alcohol in the 1,000 c.c. flask in which the precipitation was originally made and making up to the 1,000 c.c. mark with alcohol; 200 c.c. of this solution should then be used. This procedure, however, is complicated by the fact that the lipoids are only soluble in hot alcohol, which makes the taking of an aliquot part a matter of some difficulty. Before finally adopting this method, therefore, it was necessary to try some control experiments. These were done as follows:—

*Control Exp. I.*—A 50-gramme sample of brain was treated in the usual way, and the lipoids, after dissolving in hot alcohol, made up to 500 c.c. While warm 200 c.c. were taken with a warm pipette and the sulphur estimated. The sulphur in the remaining 300 c.c. of the solution was then also estimated. The yields were 24.0 mg. and 36.0 mg.  $BaSO_4$  respectively, which figures are in the proportion of 200:300.

*Control Exp. II.*—From three 100-gramme samples of three brains the lipoids were made up to 1,000 c.c. and 200 c.c. aliquot parts taken. From these same brains 20-gramme samples of material were collected, and the sulphur in the total lipoids estimated without taking an aliquot part. The following table gives the results:—

CASE NO.	BARIUM SULPHATE		S. CALCULATED IN PER CENT. OF DRY MATTER.	
	Aliquot part.	20 grm. sample.	Aliquot part.	20 grm.
19 .....	51.8 mg.	43.7 mg.	0.154 .....	0.135
28 .....	33.4 mg.	31.6 mg.	0.102 .....	0.097
42 .....	43.5 mg.	42.0 mg.	0.125 .....	0.121

The agreement is better in the last two samples which were estimated at a later time when more experience had been acquired in taking the aliquot part. There is a tendency for the aliquot part to come out

higher; this can no doubt be accounted for by the cooling of the liquid in the pipette, and must be avoided as much as possible.

*Control Exp. III.*—Seventy-seven grammes of blood which should contain no lipoid sulphur were treated in the same way. All the lipoid precipitate was destroyed and gave no weighable quantity of barium sulphate. Water soluble organic and inorganic sulphates do not, therefore, adhere to the lipoid precipitate in sufficient amount to account for the quantities found. This experiment serves as a negative control.

*Details of method.*—After the lipoid precipitate has been allowed to drain and the volume of the filtrate recorded, the funnel is placed in the litre flask originally used and a hole punched in the bottom of the filter paper with a glass rod. By means of a hot alcohol wash bottle all the sticky mass adhering to the filter paper and to the glass rod is completely washed into the flask. It is better to use 95 per cent. alcohol for this. The amount of alcohol in the flask should now be 400–600 c.c.; the bulk is made up to about 900 c.c. with absolute alcohol and the whole warmed on a water bath until complete solution has taken place. Great care must be taken that the sticky mass, which has a tendency to adhere to the bottom of the flask and which may easily be missed as it is rather transparent, has been completely dissolved. The shaking of the flask must also be carefully done, as too violent shaking may cause the liquid to boil over and thus spoil the analysis. When everything appears to have dissolved, enough warm alcohol is added to make the bulk 1,000 c.c. While keeping the flask on the water bath, a 100 c.c. pipette is now introduced, and by carefully drawing up the liquid and allowing it to again flow back into the flask, at the same time turning the flask, a uniform mixture can be obtained. This treatment at the same time warms the pipette. 200 c.c. are removed as carefully and rapidly as possible, evaporated to a semi-pasty condition and then mixed with fusion mixture.

It is perfectly futile to attempt the destruction of this organic matter with less than 40 grammes of fusion mixture distributed between three silver crucibles of the size previously described. The difficulties experienced at this point will soon convince anyone how practically impossible it would be to try to burn all the lipoid precipitate in this manner instead of taking an aliquot part. There seems to be an unnecessary amount of detail in this description, but we feel convinced that anyone attempting to repeat these analyses with any aim at accuracy would wish there had been more, as the factors which from time to time tended to spoil analyses seemed almost infinite.

*Estimation of S<sub>2</sub>.*—The water solution filtered from the lipoid precipitate is evaporated to moist dryness, mixed with 10 grammes fusion

mixture and the sulphur estimated. In adding the fusion mixture care must be taken to prevent excessive spattering due to the liberation of  $\text{CO}_2$  by the acid present. It is also well *not* to heat this estimation to as high a temperature with the Barthel burner as the others, on account of the fact that the larger amount of sodium chloride present is liable to cause it to cake, also the sodium chloride is liable to attack the silver crucibles and bring about the formation of a colloidal form of silver chloride in the final solution, and this spoils the neatness of the barium sulphate precipitation. It might also be advisable to use a platinum crucible for this estimation.

*Estimation of  $S_2^I$ .*—The filtrate from a second 100-gramme sample is evaporated to about 300 c.c., filtered, if necessary, and the sulphates estimated directly by barium chloride. The weighings of barium sulphate here amount to about 12–15 mg. Too much confidence must therefore not be placed in this result; it is better to regard it in the nature of a correction, by means of which it is possible to estimate the organic part of the  $S_2$  fraction. Sulphates appear to be eliminated from the tissues as rapidly as they are formed, so that the amount present at any time is never very great and the variations are of comparatively little significance (3–4 per cent. of total S).

*Estimation of  $S_3$  and  $S_4$ .*—The protein residue insoluble in alcohol is dried, weighed, and allowed to come into equilibrium with the moisture of the air as previously described. One gramme is then taken, mixed with 12 grammes fusion mixture and the sulphur estimated. Great care must be taken *not* to hurry the preliminary burning, as sulphur may be lost on account of the dry nature of the material. The result represents  $S_{3+4}$ . The remainder of the protein residue is then extracted with hot water (p. 190), the extracts evaporated and mixed with 10 grammes fusion mixture. This result represents the  $S_3$ , and subtracted from the  $S_{3+4}$  gives the  $S_4$  or protein fraction.

*Estimation of  $S_3^I$ .*—From another 100-gramme sample the eight hot-water extracts of the alcohol insoluble residue are evaporated with 5 c.c. conc. HCl to 300 c.c., filtered if necessary, and the sulphates estimated directly with barium chloride. It is a question whether  $S_{3+4}$  minus  $S_3$  or  $S_{3+4}$  minus  $S_3^I$  more accurately represents the protein sulphur. The portion of  $S_3$  of organic nature usually amounts to about 5 per cent. of the total sulphur, and is mainly precipitated by phosphotungstic acid. The amounts, however, are so small that their investigation will be a matter of some difficulty; in recording the analyses in this paper, therefore, the latter figure  $S_{3+4}$  minus  $S_3^I$  is invariably referred to as the protein or rather protein-like sulphur.

*Method of keeping analytical records and calculation of results.*—The



method of notation here used has already been explained, and it seemed of interest to describe in a little more detail not only the method of calculating the results but also a method of keeping laboratory notes on the card catalogue system, which may be of general value in investigations of this kind. The copy of a card from one of the cases with analytical results and calculation in logarithms follows:—

CASE 70. C. E. S. Age 43. Dept. of Path. Material collected 5.1.08. Univ. of Chicago. Analysis begun 8.1.08.						
100 g. 10 HCl, 15 CHCl <sub>3</sub> , 2 days $\frac{830}{1000}$ filt.	S <sub>1</sub>	S <sub>2</sub>	S <sub>3+4</sub>	S <sub>5</sub>	S <sub>2</sub> <sup>I</sup>	S <sub>3</sub> <sup>I</sup>
S <sub>1</sub> gave (44.1 × 5) mg. BaSO <sub>4</sub>	9129	7642	7267	6435	0769	0969
S <sub>2</sub> „ (58.1 × $\frac{985}{710}$ ) mg. BaSO <sub>4</sub>	1903	8513	1377	1377	8808	1377
Protein residue weighed 9.671 air dry	1032	9129	9854	9854	1961	2346
S <sub>3+4</sub> 1.000 g. air dry gave 53.3 mg. BaSO <sub>4</sub>	3177	1377	8498	7666	1377	0425
S <sub>5</sub> 8.671 g. „ „ „ 44.0 „ „	1377	9934	0425	9381	9934	1921
100 g. 10 HCl, 15 CHCl <sub>3</sub> , 3 days $\frac{760}{1000}$ filt.	4554	0440	8073	8285	3272	
S <sub>2</sub> <sup>I</sup> gave 12.0 × $\frac{985}{760}$ mg. BaSO <sub>4</sub>	0425	0425		0425	0425	
S <sub>3</sub> <sup>I</sup> gave 12.5 mg. BaSO <sub>4</sub>	4129	0015		7860	2847	
	S <sub>1</sub>	S <sub>2</sub>	S <sub>3+4</sub>	S <sub>5</sub>	S <sub>2</sub> <sup>I</sup>	S <sub>3</sub> <sup>I</sup>
	25.9%	10%	64.2%	6.1%	1.9%	1.5%

*Explanation of card.*—The first 100 gramme sample was extracted and the alcohol residue after emulsifying precipitated with 10 c.c. HCl and 15 c.c. CHCl<sub>3</sub> and made up to 1,000 c.c. After standing for two days, filtered, and the volume of filtrate 830 c.c. recorded, 710 c.c. of this filtrate were evaporated and gave 58.1 mg. BaSO<sub>4</sub>. The aliquot part of the lipoids (200 c.c. of 1,000 c.c.) gave 44.1 mg. BaSO<sub>4</sub>. The calculation is as follows:—

<u>S<sub>2</sub></u>				<u>S<sub>1</sub></u>			
log 58.1	...	...	7642	log for S <sub>1</sub> in 1 c.c.	...	...	9129
log 710	...	...	8513	log 155 (filtrate clinging to lipoids).	...	...	1903
S <sub>2</sub> in 1 c.c.	...	...	9129	Correction for S <sub>1</sub>	...	...	1032
log BaSO <sub>4</sub> to S	...	...	1377	Antilog for correction	...	...	12.7 mg.
log 985 (total filtrate)	...	...	9934	(44.1 × 5) — 12.7 =	...	...	207.8 mg.
			0440	log 207.8 (actual S after corr.)	...	...	3177
log for total S	...	...	0427	log BaSO <sub>4</sub> to S	...	...	1377
S <sub>2</sub> in % of total S	...	...	0013				4554
Antilog	...	...	10.0%	log for total S	...	...	0427
				S <sub>1</sub> in % of total S	...	...	4127
				Antilog	...	...	25.9%
<u>S<sub>3+4</sub></u>				Calculation of total S.			
log 53.3	...	...	7267	Antilog 0440	...	...	1107
log BaSO <sub>4</sub> to S	...	...	1377	.. 4554	...	...	2852
log 9.671	...	...	9854	.. 8498	...	...	7076
			8498				11035
log for total S	...	...	0427				
log S <sub>3+4</sub>	...	...	8071				
Antilog	...	...	64.2%	log 11035 (total S) is 0427.			

The other calculations follow on the principles here outlined, and should be easily understood.  $S_2^I$  and  $S_3^I$  were done on second 100-gramme sample. It will be evident that by thus expressing the results in per cent. of total sulphur the water estimation does not need to be taken into account. In several cases the total S in per cent. of dry tissue was estimated directly on a sample of brain matter and found to check that obtained by calculation from the different fractions. The phosphorus estimations were recorded in similar ways on cards of a different colour, and were calculated in practically the same way as here described.

#### ESTIMATION OF PHOSPHORUS.

*Outline of method.*—In order not to multiply needlessly the work, a method of estimating phosphorus was adopted which could be applied to the same material used for the sulphur estimations. For this purpose the filtrate from the  $BaSO_4$  precipitate, which should contain all the phosphorus as phosphoric acid, was treated with ferric chloride and ammonia. In order to test if this method removed all the phosphorus as iron phosphate, controls were made with the filtrates, and these indicated that the precipitation has to be repeated in order to ensure complete removal. The following results will illustrate this:—

Case.	First Fe ppt. contained	Second Fe ppt. contained
42 $P_1$ ..	148.8 mg. $Mg_2P_2O_7$ ..	8.1 mg. $Mg_2P_2O_7$ ..
15 $P_2$ ..	65.4 " " ..	5.6 " " ..
15 $P_1$ ..	143.4 " " ..	12.9 " " ..
42 $P_2$ ..	94.8 " " ..	13.8 " " ..

The use of a greater amount of iron in the first place does not obviate this difficulty. Another source of error in this method lies in the fact that on account of the large amount of iron used, the magnesium pyrophosphate precipitates are very apt to show a slight iron stain. No amount of washing or control of the amount of iron can obviate this, as the iron seems to enter into the complex molecule of the ammonium phosphomolybdate as a component part. However, the following results indicate that the error is not great and is well within the variations of the material:—

Case.	$Mg_2P_2O_7$ mg.	Fe mg.	Percentage error.
19 $P_1$ .....	92.4 .....	1.4 .....	1.4
30 $P_2$ .....	144.2 .....	1.3 .....	1.0
70 $P_2$ .....	169.8 .....	2.5 .....	1.5
29 $P_2$ .....	207.7 .....	1.0 .....	0.5
70 $P_1$ .....	57.4 .....	0.5 .....	1.0

The iron was estimated colorimetrically with KCNS by comparison with an iron solution of known strength. It is not necessary to enter into the

details of this method here as the usual errors would not very seriously affect the above observations.

*Details of method.*—To filtrate from  $\text{BaSO}_4$  precipitation add from 1–3 c.c. of a 20 per cent. ferric chloride solution. Add 5–10 c.c. ammonia, sufficient to make an excess, boil until the fumes of ammonia are no longer given off and then filter. To the filtrate add again 1 c.c. ferric chloride solution and repeat precipitation. Place the funnel containing the two precipitates in the flask in which the precipitation has been made, punch a hole in the bottom of the filter paper with a glass rod, and wash the precipitate into the flask with hot water. The filter paper is then moistened with 1 c.c. nitric acid and washed until all traces of iron are removed. Another cubic centimetre of nitric acid is usually sufficient to dissolve the whole precipitate. It is necessary to effect this transference while the precipitate is quite moist, as it becomes hard and insoluble in nitric acid on standing. In the  $P_1$  and  $P_2$  estimations it is desirable at this point to filter the solution and to take an aliquot part (*e.g.*, 150 of 250 c.c.), for the amount of phosphorus in these fractions is comparatively large, and the precipitates obtained are too bulky to manipulate neatly; also good re-agents may be wasted unnecessarily.

In this solution the phosphorus is estimated in the usual way (30) with nitro-molybdate solution in the presence of an excess of ammonium nitrate. All estimations recorded in this communication were finally weighed as  $\text{Mg}_2\text{P}_2\text{O}_7$ .

*Estimation of  $P_1$ .*—This fraction is estimated in the filtrate from the  $S_1$  precipitation, and a correction applied for  $P_2$  in the same manner as in the  $S_1$  calculation. The method devised by Koch and Woods (30) for the separation of lecithin and kephalin has been found to vary so much with the conditions of the experiment that the results seem hardly reliable.

*Estimation of  $P_2$ .*—This estimation is made on the filtrate of the  $S_2$  barium sulphate precipitation. With regard to the estimation of  $P_1^I$  the results have been uncertain. Grindley (31) has attempted the separate estimation of inorganic and organic combined phosphates, but it does not appear to us at all certain that his method may not break up organic radicles. One experiment was made to estimate the phosphates directly in this fraction with magnesia mixture. The results are as follows:—

	$P_2$ BY FUSION IN PER CENT. OF TOTAL P.	$P_1^I$ DIRECT BY MAGNESIA MIXTURE.
Case 26	11.4	5.2

There does appear to be present a considerable amount of organically combined phosphates which are not broken up by this method.

*Estimation of  $P_3$ .*—This fraction seems to consist entirely of  $P_3^i$  inorganic phosphates, unless we are here again dealing with the breaking up of organic radicles:—

PHOSPHORUS BY FUSION.				P. BY DIRECT PPTN WITH NITRO-MOLYBDATE.	
Case 26	...	...	9.8	.....	9.9
Case 70	...	...	10.6	.....	10.5

In recording the results  $P_2$  and  $P_3$  are added together under the term extractive phosphorus.

*Estimation of  $P_4$ .*—The residue after extraction with hot water is burned by Neumann's method and the phosphorus estimated in the usual way. The very great variations observed in the results obtained by this method, still further emphasise the difficulties of estimating milligrammes of phosphorus in grammes of organic material.

#### ESTIMATION OF WATER.

The amount of blood in the tissues at death and the accidental and almost uncontrollable variations in the amount of drying during the collection of the material are apt to introduce differences in the water content of various brains, and for these reasons not much importance has been attached to the comparatively slight variations which occur with some normal and pathological brains. It is, however, necessary to estimate the water content in an investigation of this kind in order to determine the various constituents in percentage of the total solids.

It has been already demonstrated (1) that it is difficult to dry to constant weight material of colloidal nature, and that the best method consists in drying in vacuo below the coagulation point of the colloid. This method has been adopted. Weighed quantities of minced brain matter have been spread out on one of two tared (paired) watch glasses fitted with a clip, allowed to remain in a vacuum desiccator for some time and then dried to constant weight in a vacuum oven at 40°–42° C. When constant weight is attained, it is found that raising the temperature to 100° C. does not materially affect the result.

Benedikt (32) has since devised a method which in principle resembles our method, but offers no special advantages.

The amount of material taken should be as near as possible 2 grammes; a larger quantity than this makes the drying a very long and tedious operation, while smaller amounts on account of their smallness may introduce error. A number of moisture determinations made in duplicate are given below, and the results not only show a fair check of accuracy of the method, but also indicate that the mincing process gives a uniform mixture of the grey and white matter, as the samples

were taken in each instance from quite distinct portions of the minced material:—

NO. OF CASE.		28.	40.	41.	29.	42.
Per cent. of moisture	{ (a)	78.61	77.41	78.38	77.52	76.68
	{ (b)	78.74	77.50	78.55	77.49	76.83

#### ESTIMATION OF GROUPS OF CONSTITUENTS.

*Proteins, extractives and ash.*—The method is essentially that outlined before (1). The proteins are calculated by subtracting the weight of the residue from the hot-water extractions from the original dry weight of the alcohol insoluble residue. The extractives are made up from the above water soluble residue and the residue from the filtrate derived from the lipid precipitation corrected for total volume. The ash is the residue obtained on incineration of the extractives at dull red heat. Not many observations are recorded in these pages, as they did not appear to show any great variations.

*Cerebrins.*—This estimation is accomplished by determining gravimetrically with Fehling's solution the amount of galactose split off with dilute HCl.

When the aliquot part of the lipid precipitate of 100 grammes brain matter is being taken for the  $S_1$  estimation another 100 c.c. (*i.e.*, one-tenth aliquot part) is taken for the cerebrin estimation. This is placed in a *litre flask* and the alcohol and chloroform *completely evaporated*. Even then, it is well to add a little distilled water and to boil for some time, for the presence of alcohol and chloroform is liable to give rise to other reducing compounds, *e.g.*, phosgene, and thus vitiate the result. A large flask is necessary, for the frothing is rather considerable, and unless this precaution is heeded will cause much annoyance. The bulk of the solution is made up to 100 c.c. and 3 c.c. HCl added. The flask is then fitted with a reflux condenser, placed on a sand bath and gently heated for at least 24 hours, not necessarily consecutive. Towards the end of the hydrolysis the solution may appear milky; it is advisable then to add a few more drops of conc. HCl, when this will disappear. The solution with washings is now transferred to a 250 c.c. graduated flask; sodium sulphate, solid or in concentrated solution, is added until all precipitation is complete and the supernatant fluid is clear and bright, then the bulk is made up to 250 c.c., the flask well shaken, and allowed to stand for a while. The solution is then filtered and an aliquot part 100–150 c.c. taken; to this, after carefully neutralising, is added 100 c.c. freshly-made Fehling's solution, and the whole stirred and placed on a water bath for four hours. At the end of that time the precipitate is collected on a Gooch asbestos filter, washed with hot distilled water, ignited and

weighed as  $\text{CuO}$ , or reduced further and weighed as metallic copper. From this weighing the equivalent amount of galactose is ascertained, and an approximation of the amount of cerebrin obtained by multiplication with 100/21.8, Thierfelder's factor for the sugar equivalent of cerebrin. The Fehling's solution must always be in considerable excess, and during the precipitation the solution should not be allowed to evaporate to any great extent.

Sugar determinations have been made on the filtrates obtained from the lipid precipitation. In each instance, after boiling off the chloroform present, no reduction occurred.

*Cholesterin.*—The method of Ritter (33) was again used in the few cholesterin determinations made in this work.

### III. ANALYTICAL RESULTS.

The above methods permit the comparison of normal and pathological material from three points of view:—

1. *Condition of nutrition of tissue.*—This considers the variations in the three principal food constituents; proteins, fats (lipoids) and carbohydrates (cerebrin).

2. *Changes in oxidations.*—It will be very difficult to draw any conclusions with regard to the intensity of oxidations from any variations in the sulphates. It appears that the sulphates, like carbon dioxide and urea, are very rapidly eliminated from the tissues and soon appear in the urine. As a result they are only found in the tissues in amounts too small to permit any conclusions based on variations (15 mg.  $\text{SO}_4$  in 100 grammes brain material). To attempt to study the oxidations by the difference in composition of the blood going to and coming from the brain, such as Hill (34) has attempted with carbon dioxide, would be quite out of the question with material which cannot be obtained until after death. It remains, therefore, to compare variations in the intermediary oxidation compound which appears to have a greater affinity for some constituents of the protoplasm, and is hence not eliminated so rapidly, *i.e.*, the taurin-like compound described by one of us (13), here referred to as neutral sulphur.

3. *Destructive changes accompanied by reparative growth.*—These changes it is proposed to study by the variations in the phosphorus. An increase in extractive phosphorus would thus indicate a period of increased growth, together with a greater supply of material from which to build up the more complex phosphoric acid derivatives. This increase in extractive phosphates may be due to increased food supply, or during destructive changes to increased breaking down of complex derivatives.

It is necessary to bear in mind, in looking over the results of these methods, that they only express a relative change. Thus if we find that the total phosphorus of a brain of a general paralytic expressed in percentage of dry matter is the same as that of the normal, it is not correct to conclude that such a brain has not lost phosphorus as the result of the destructive changes which we know have taken place. It merely means that the relative proportion has not changed. In expressing the results for the various groups in the sulphur and phosphorus derivatives, it seemed better to give them in percentage of total phosphorus and sulphur. This eliminates a number of errors and permits of a very good comparison of the different samples with one another, besides enabling the comparison of these results with analyses made by other investigators. A great many interesting investigations of pathological material are vitiated by lack of attention to this point. The system of notation used in the analytical work and there explained is here translated into terms which are more familiar:—

*Protein sulphur* represents  $S_3 + 4$ , minus  $S_1^1$ .

*Lipoid sulphur* represents  $S_1$ .

*Neutral sulphur* represents  $S_2$  minus  $S_2^1$ .

*Inorganic sulphur* represents  $S_2^1$  plus  $S_3^1$ .

An explanation may not be out of place for the term neutral sulphur. It represents a combination of sulphur which does not split off sulphuric acid on prolonged boiling with hydrochloric acid, neither does it form lead sulphide on boiling with alkali and lead acetate. The term neutral is used in contradistinction to sulphates or sulphuric acid, and represents merely a makeshift until the chemical nature of this compound or group of compounds can be more definitely established.

Phosphorus group:—

*Protein phosphorus* represents  $P_4$ .

*Lipoid phosphorus* represents  $P_1$ .

*Extractive phosphorus* represents  $P_2$  plus  $P_3$ .

It seems much better to express the results in this manner than to attempt to calculate protein phosphorus into nucleo-proteins or lipoid phosphorus into lecithin, until we know a great deal more of the chemical nature of these compounds, which at present can only be designated as rather indefinite groups. In a few tables for better comparison the lecithin and kephalin were occasionally calculated from the lipoid phosphorus by multiplication with the factor 25.77.

The word *extractive* in these investigations is used on the old basis originally intended by Liebig when he used the term. It has become the custom of some investigators to refer to lipoid phosphorus as extractive,

because it is extracted with alcohol. This is incorrect, and only brings confusion to the term originally used.

*Changes with age.*—We will first consider the variations in the relative composition of the nervous system at different ages. A preliminary report of this subject we gave to the Physiological Society (25):—

### COMPARISON OF BRAINS AT DIFFERENT AGES.

TABLE I.

	CASE 13.	CASE 14.		CASE 15.	
	Age, 6 weeks ? Weight, 640 grammes.	Age, 2 years ? Weight, 1100 grammes		Age, 19 years ♂ Weight, 1670 grammes.	
	Whole brain.	Cortex.	Corpus. callosum.	Cortex.	Corpus. callosum.
Proteins ... ..	46.6	48.4	31.9	47.1	27.1
Extractives ... ..	12.0	10.0	5.9	9.5	3.9
Ash ... ..	8.3	5.8	3.2	5.9	2.4
Lecithins and kephalins ...	24.2	24.7	26.3	23.7	31.0
Cerebrins ... ..	6.9	8.6	17.2	8.8	18.3
Lipoid S. as SO <sub>4</sub> ... ..	0.1	0.1	0.5	0.1	0.5
Cholesterin (by diff.) ...	1.9	2.4	15.0	4.9	16.8
Total S. ... ..	0.52	0.53	0.63	0.46	0.50
Total P. ... ..	1.72	1.50	1.46	1.45	1.45
Moisture ... ..	88.78	84.49	76.45	83.17	69.67

#### *Distribution of Sulphur in per cent. of total S.*

Protein S. ... ..	62	63	55	76.5	56
Lipoid S. ... ..	6	6	27	7	36
Neutral S. ... ..	26	22	13	10	5
Inorganic S. ... ..	6	9	5	6	3.5

#### *Distribution of Phosphorus in per cent. of total P.*

Protein P. ... ..	5	6	6	5	5
Lipoid P. ... ..	54	62	72	63	81
Extractive P. ... ..	41	32	22	32	15



Two additional cases were studied, and are given in the following table compared with Case 13:—

TABLE II.

	CASE 13.	CASE 19.	CASE 70.
	Age, 6 weeks ? Weight, 640 grammes.	Age 24 years ♂ Weight, 1280 grammes.	Age 43 years ♂ Weight, 1400 grammes.
	Whole brain.	Whole brain.	Whole brain.
Protein S. ....	62	60	62.5
Lipoid S. ....	6	27	26
Neutral S. ....	26	9.5	8
Inorganic S. ....	6	3	3.5
Protein P. ....	5	4	6
Lipoid P. ....	54	73	75
Extractive P. ....	41	23	19

In the above tables is to be observed with the growth of the brain:—

1. A decrease in moisture, proteins, extractives, and ash, a change usually found in growing tissues.

2. An increase in cerebrin, lipoid-sulphur and cholesterin; in other words, the substances which predominate in the white matter. As far as they go, our results on the younger brains are in harmony with the work of Kaes (35) on the influence of age on the myelination of fibres, but the number of cases, especially senile cases, is not sufficient to permit of any close correlation with his observations.

In connection with the changes due to age, it seems of interest to compare a brain of lower anatomical development. A comparison of the brain of the dog and human follows:—

TABLE III.

COMPARISON OF BRAIN OF HUMAN AND DOG.

	DOG (1). Weight... 75 grammes. Whole brain.	HUMAN (Case 19). 1,230 grammes. Whole brain.
Protein S. ....	73	60
Lipoid S. ....	18	27
Neutral S. ....	6	9.5
Inorganic S. ....	3	3
Protein P. ....	4.5	4
Lipoid P. ....	70	73
Extractive P. ....	25.5	23
MOISTURE ....	78.1	77.9
TOTAL P. ....	1.50	1.50
TOTAL S. ....	0.45	0.50

The agreement in the phosphorus is quite close. The variation in the lipoid and neutral sulphur will be discussed at a later date when an investigation of a series of brains from different animals which is to be undertaken by one of us, has been completed.

*Changes involved by reason of the nature of the cause of death:—*

The variations that may be introduced by *post-mortem* change have already been discussed (p. 185). As a good many of the mental cases here studied died of tuberculosis, it appeared of interest to compare three normal brains, one of which was from a case of tuberculosis, the others from cases which had died of other causes.

TABLE IV.—COMPARISON OF BRAINS OF CASES DYING FROM DIFFERENT CAUSES.

Cause of Death...	CASE 15.		CASE 19.			CASE 70.
	<i>Slow Hemorrhage.</i>		<i>Tuberculosis.</i>			<i>Diffuse suppurative meningitis.</i>
	Cortex.	Corpus callosum.	Cortex.	Corpus callosum.	Whole brain.	Whole brain.
Protein S. ....	76.5	56	75.0	54	60	62.5
Lipoid S. ....	7.0	36	7.0	36	27	26
Neutral S. ....	10.0	5	12.0	6.5	9.5	8
Inorganic S. ....	6	3.5	5.5	3	3	3.5

In spite of the great difference in the cause of death (a chronic, an acute infection, and a simple loss of blood) the results are fairly uniform, and are within experimental error. They also indicate that variations in the amount of blood in the brain at death do not introduce an appreciable error.

#### CHANGES OBSERVED IN MENTAL CASES.

(a) The cases chosen were those in which a clinical diagnosis of dementia præcox was given. The results are as follows:—

TABLE V.—VARIATIONS IN THE PROXIMATE CONSTITUENTS.

	Cortex		Corpus callosum.	
	CASE 15 Normal.	CASE 17. Dementia Præcox.	CASE 15. Normal.	CASE 17. Dementia Præcox.
Protein ...	47.1	49.4	27.1	27.8
Extractives ...	9.5	7.7	3.9	3.0
Ash ...	5.9	5.5	2.4	2.7
Lecithin and Kephalin ...	23.7	23.0	31.0	29.7
Cerebrins ...	8.8	9.3	18.3	20.2

The only change of any magnitude involves a decrease of the extractives to which attention has already been drawn by one of us (36) in a previous paper.

TABLE VI.  
COMPARISON OF CORTEX AND CORPUS CALLOSUM OF TWO NORMAL BRAINS AND TWO BRAINS OF DEMENTIA PRÆCOX.

	NORMAL.			DEMENTIA PRÆCOX.			AVERAGES.		PERCENTAGE VARIATION FROM NORMAL.
	Case 15.	Case 19.	Percentage variation.	Case 17.	Case 30.	Percentage variation.	Normal.	Dementia Præcox.	
				<i>Cortex.</i>					
Protein S. ...	76.5	75.2	1.6 per cent.	81.1	77.3	4.2 per cent.	75.8	79.2	+ 4.5
Lipoid S. ...	7.0	7.1	0.0	8.7	9.2	5.5	7.1	8.9	+25.7
Neutral S. ...	10.0	12.2	20.0	5.4	8.7	47.0	11.1	7.0	-37.3
Inorganic S. ...	6.4	5.4	16.6	4.7	4.7	0.0	5.9	4.7	-20.0
				<i>Corpus Callosum.</i>					
Protein S. ...	55.8	54.1	3.1 per cent.	58.0	55.6	4.2 per cent.	54.9	56.8	+ 3.5
Lipoid S. ...	36.1	35.9	0.0	35.6	37.4	5.0	36.0	36.5	+ 1.4
Neutral S. ...	4.6	6.5	34.5	2.7	3.2	16.6	5.5	3.0	-45.4
Inorganic S. ...	3.5	3.3	6.0	3.8	3.8	0.0	3.4	3.8	+11.7

TABLE VII.  
COMPARISON OF THE CHEMICAL COMPOSITION OF THE WHOLE BRAIN FROM TWO NORMAL CASES AND FOUR CASES OF  
DEMENTIA PRÆCOX.

	NORMAL.		DEMENTIA PRÆCOX.					AVERAGES.		Percentage variation from normal.
	Case 19.	Case 20.	Percentage variation.	Case 28.	Case 29.	Case 41.	Case 42.	Normal.	Dementia Præcox.	
Protein S ...	60.2	55.8	7.6 per cent.	64.7	59.7	65.0	66.7	58.0	64.0	+ 10.3
Lipoid S ...	27.1	32.1	16.6 "	24.6	28.8	23.0	24.8	29.6	25.3	- 14.0
Neutral S ...	9.5	8.8	7.7 "	5.0	5.6	6.1	3.3	9.2	5.0	- 46.7
Inorganic S ...	3.3	3.3	0.0 "	5.6	5.9	5.9	5.2	3.3	5.6	+ 40.0
Total S in per cent. of dry matter ...	...	...	...	...	...	...	...	0.48	0.48	0.0
Protein P ...	3.7	4.7	25.0 "	3.8	5.1	3.6	4.7	4.2	4.3	0.0
Lipoid P ...	73.1	70.3	3.9 "	73.7	73.0	73.6	70.8	71.7	72.8	+ 1.5
Extractive P ...	23.2	25.1	8.0 "	22.6	21.9	22.9	24.4	24.1	22.9	- 5.2
Total P in per cent. of dry matter ...	...	...	...	...	...	...	...	1.50	1.42	- 5.0

The largest percentage variation is found in the neutral sulphur. It varies in the cortex of the two cases of dementia præcox among themselves, but in each instance it is lower than in the normal cortex. The variations in the inorganic sulphates are of little value on account of the small amounts, the estimations amounting in reality to a correction only. The proportionate amounts of neutral sulphur are not much greater, but in order to confirm the results analyses were made on 100-gramme samples of a minced hemisphere.

The variation in the total sulphur and phosphorus are within the limits of error. The largest variation again is the decrease of neutral sulphur, and the next largest the increase of sulphates. The increase in sulphates may not necessarily be of significance, as the actual quantities were very small and consequently liable to analytical error; this, however, was not the case in the neutral sulphur estimations. Although the variations in the neutral sulphur of the pathological cases among themselves are considerable, they are all in the same direction, and consequently of a consistent nature.

The absence of variations in the phosphorus fractions is striking.

(b) *Dementia paralytica*.—This form of insanity was selected to serve as a control of the analytical technique of the adolescent cases:—

TABLE VIII.

VARIATIONS IN THE PROXIMATE CONSTITUENTS.

	CORTEX.		CORPUS CALLOSUM.	
	Case 15 Normal.	Case 16 G. P.	Case 15 Normal.	Case 16 G. P.
Proteins ... ..	47.1	50.7	27.1	30.0
Extractives ... ..	9.5	7.6	3.9	3.7
Ash ... ..	5.9	6.0	2.4	3.2
Lecithins and kephalins ...	23.7	23.9	31.0	25.0
Cerebrins ... ..	8.8	9.4	18.3	18.2

There is an increase in proteins probably correlated to the growth of glia tissue, a decrease in extractives in the cortex and a very marked decrease in the lecithin and kephalin of the corpus callosum. The latter decrease is not so well demonstrated in the following cases, in which uniform samples of a whole hemisphere were analysed. However, there is a tendency for the lipid phosphorus to be decreased.

TABLE IX.  
COMPARISON OF THE CHEMICAL COMPOSITION OF THE BRAINS OF TWO NORMAL CASES AND FOUR CASES OF GENERAL PARALYSIS.

	NORMAL.			GENERAL PARALYSIS.					AVERAGES.		Percentage variation from normal.	
	Case 18.	Case 70.	Percentage variation.	Case 22	Case 23.	Case 24.	Case 40.	Maximum percentage variation.	Normal.	General paralysis.		
Protein S	...	60.9	62.6	2.7 per cent.	56.7	57.1	62.0	61.4	9.0 per cent.	61.7	59.3	—3.9
Lipoid S	...	28.6	25.9	10.0	30.2	30.8	25.1	28.4	21.0	27.2	28.6	+5.2
Neutral S	...	7.2	8.1	11.5	9.3	8.3	9.1	6.4	35.0	7.7	8.3	+8.0
Inorganic S	...	3.3	3.4	3.0	—	3.7	—	—	—	3.4	3.7	+9.0
Total S in per cent. of total solids	...	...	...	...	...	...	...	...	...	0.50	0.48	—4.0
Protein P	...	3.9	5.7	38.0 per cent.	5.9	4.8	4.6	4.6	26.0 per cent.	4.8	5.0	+4.0
Lipoid P	...	71.8	75.0	4.4	69.3	70.6	68.2	69.9	3.4	73.4	69.5	—5.3
Extractive P	...	24.2	19.4	21.6	24.7	24.7	26.9	25.6	8.5	21.8	25.5	+17.0
Total P in per cent. of total solids	...	...	...	...	...	...	...	...	...	1.45	1.46	0.0

The variations from the normal here are remarkably slight. It is especially interesting to note that, with one exception, the neutral sulphur is not decreased. This distinguishes these cases from those of dementia præcox, and also serves as a control of the analytical technique. Although the lipid phosphorus has a decided tendency to be decreased with a corresponding increase of the extractive phosphorus, the variation is not so striking as might be expected. The increase in nuclein phosphorus observed by one of us (W. K.) and Goodsen (37) is apparently not present in all cases.

(c) *Other cases of mental disorder.*—As a further test of the methods two mental cases with the clinical diagnosis of melancholia were taken for analysis. The results are given in the following table:—

TABLE X.

COMPARISON OF THE BRAINS OF TWO NORMAL CASES AND TWO CASES OF MELANCHOLIA.

	NORMAL.		MELANCHOLIA.		AVERAGES.		PERCENTAGE VARIATION.
	Case 18.	Case 70.	Case 25.	Case 26.	Normal.	Pathological.	
Protein S. ... ..	60.9	62.6	57.4	56.9	61.7	57.2	— 7.0
Lipoid S. ... ..	28.6	25.9	29.7	32.4	27.2	31.0	+ 13.9
Neutral S. ... ..	7.2	8.1	9.3	7.0	7.7	8.1	+ 5.2
Inorganic S. ... ..	3.3	3.4	—	—	3.4	—	—
Protein P. ... ..	3.9	5.7	4.2	4.1	4.8	4.2	— 15.0
Lipoid P. ... ..	71.8	75.0	69.2	74.7	73.4	72.0	— 2.0
Extractive P. ... ..	24.2	19.4	26.6	21.2	21.8	23.9	+ 10.0

The variations are comparatively slight, and permit of no conclusions that would not be vitiated by differences due to the material or the analytical technique. The sulphates were not estimated in the two pathological cases, and the neutral and protein sulphur correction was applied according to the results of other cases.

#### EXPERIMENTAL CHANGES (with Dr. F. H. Pike).

As the results in dementia præcox might be interpreted as representing a reduced oxidation, some experiments were undertaken with Dr. F. H. Pike, of the University of Chicago, to study the effect of cutting off the four arteries (two carotids and two vertebrals) from the brain of a dog. As Mott and Hill have shown (38), if the animal recovers at all from the operation the recovery is complete. Such proved to be the case in the cases of which the analyses are given in the following table:—

TABLE XI.

		Dog (2)	Dog (3)
		Weight of brain 46.08 grammes.	51.38 grammes.
		3 days after operation.	2 months after operation.
Protein S. ... ..	...	73.9	73.9
Lipoid S. ... ..	...	16.1	16.0
Neutral S. ... ..	...	7.1	6.9
Inorganic S. ... ..	...	2.9	3.2

The first case serves as a control, for it is hardly likely that an organ which has such a special metabolism as the brain would change in a few

days. The results show no variation at all, and give a very good idea of the accuracy to be expected from the methods outlined in this paper.

#### IV. DESCRIPTION OF CASES.\*

*Case 13.*—S. H., Evelina Hospital, London, 7/11/06. Female; age six weeks. Autopsy 24 hours after death.

*Weight of brain.*—640 grammes. White matter had not differentiated sufficiently to be capable of microscopic separation. Whole right hemisphere, after removing basal ganglia, used for chemical analyses. On account of the premature birth this brain is very much under developed for its age.

*Cause of death.*—Prematurely born; died from inanition.

*Case 14.*—E. McC., Evelina Hospital, London, 8/12/06. Female, age 1 year 11 months. Autopsy ten hours after death.

*Weight of brain.*—1,100 grammes.

*Cause of death.*—Exhaustion following (two days after) operation for umbilical hernia. No evidence of peritonitis.

*Case 15.*—R. A. G., Dept. of Path. Univ. of Chicago. 199 M. March 7th, 1907. Male, age 19 years. Autopsy seven hours after death.

*Weight of brain.*—1,670 grammes. No wasting; no excess of fluid. Very anæmic. The Betz cells are perfectly normal. Many of the cells of the other cortical layers are somewhat swollen (cell body and nucleus), and show slight chromatolysis. The change is similar to the one observed experimentally with lack of oxygen. In no case, however, is there any gross change. The cells of the prefrontal area appear to be normal.

*Cause of death.*—Hæmorrhage from right internal carotid artery, following erosion by peritonsillar abscess. Death occurred as a result of continuous bleeding two days after onset.

*Mental state.*—Normal and of good order of intellect.

*Previous occupation.*—Student in high school.

*Case 16.*—C. T., Claybury Asylum. 46.M.06/2. Male, age 46 years. Autopsy 24 hours after death, body kept in cold chamber.

*Weight of brain.*—1,230 grammes. Much wasting, large excess of fluid. In the prefrontal region great destruction of nerve cells. Vessels greatly thickened. Marked neuroglia proliferation and all characteristic changes of general paralysis.

*Cause of death.*—Acute pulmonary tuberculosis.

\* Numbers in continuation of cases previously published.



*Diagnosis of mental state.*—General paralysis of the insane, with progressively slow dementia.

*Previous occupation.*—Labourer.

*Length of time in Asylum.*—Seven months.

*Case 17.*—H. F. R., Claybury Asylum. 36.M.06/2. Male, age 20 years. Autopsy nine hours after death.

*Weight of brain.*—1,645 grammes. Excess of cerebrospinal fluid (S=18 parts per million; P=160 parts). Some wasting. The nerve cells (except the Betz cells) throughout the cortical layers in ascending frontal and parietal region, except for a little swelling, are normal. Most of the Betz cells in the ascending frontal are somewhat swollen and show definite chromatolysis, most often perinuclear. Some of the Betz cells are quite normal. The neuroglia cells are swollen and show some evidence of recent proliferation.

*Cause of death.*—Pulmonary tuberculosis.

*Diagnosis of mental state.*—Dementia Præcox.

*Previous occupation.*—French polisher.

*Length of time in Asylum.*—2½ years.

*Case 18.*—A R., Charing Cross Hospital, London. M./07. Male, age 49 years. Autopsy 17 hours after death.

*Weight of brain.*—1,270 grammes. No wasting. Nerve cells normal. Some proliferation of the blood vessel walls.

*Cause of death.*—Pulmonary tuberculosis.

*Diagnosis of mental state.*—Normal.

*Previous occupation.*—Commission agent.

*Case 19.*—W. D., Brompton Hospital, London. M./07. Q.p.31. Male, age 24 years. Autopsy 19 hours after death.

*Weight of brain.*—1,230 grammes. Convolutional pattern good. No wasting. Most of the nerve cells are normal, although a considerable number show chromatolysis, without much destructive change. Some Betz cells show chromatolysis which is generally perinuclear, and resembles that observed in dementia præcox. There is some slight vascular and neuroglia proliferation.

*Cause of death.*—Pulmonary tuberculosis. Duration of disease 18 months, in hospital three months.

*Diagnosis of mental state.*—Normal.

*Previous occupation.*—Printer.

*Case 20.*—A. C. C., St. Thomas's Hospital, London. M./07. Male, age 16 years. Autopsy 30 hours after death, body kept in cold chamber.

*Weight of brain.*—1,440 grammes. No wasting. The nerve cells in

pyramidal layer are very irregularly arranged, a fair number show various stages of chromatolysis, but most are of normal appearance. There is also some evidence of destructive change in the cells of the pyramidal layer. The Betz cells show less change than those of the previous case. The vessel walls are thickened, and there is a moderate amount of vascular and neuroglia proliferation (more than in Case 19). The pia is swollen and thickened and the vessels of the pia and cortex generally are congested. On account of the histological appearance the case might be mistaken for early G. P. (Dr. Helen Stewart).

*Cause of death.*—Tuberculosis of lungs and intestines. Two months in hospital. History of tuberculosis in family.

*Diagnosis of mental state.*—Normal. Physiognomy of a low type.

*Previous occupation.*—Hall boy.

*Case 22.*—E. J. B., Claybury Asylum. 123.M.07. Male, age 37 years. Autopsy four hours after death.

*Weight of brain.*—1,190 grammes. Microscopic examination revealed characteristic changes of general paralysis.

*Cause of death.*—Exhaustion of G. P. I. Congestion and œdema of lungs.

*Diagnosis of mental state.*—General paralysis of the insane.

*Previous occupation.*—Plumber.

*Length of time in Asylum.*—Fifteen months.

*Case 23.*—M. A. P., Claybury Asylum. 5.F.0712. Female, age 40 years. Autopsy 17 hours after death.

*Weight of brain.*—1,055 grammes. Some general wasting. Microscopic examination revealed characteristic changes of G. P. I.

*Cause of death.*—Acute pulmonary tuberculosis.

*Diagnosis of mental state.*—General paralysis of the insane.

*Previous occupation.*—Fur hand.

*Length of time in Asylum.*—Two years nine months.

*Case 24.*—C. B., Claybury Asylum. 6.F.07/2. Female, age 44 years. Autopsy one hour after death.

*Weight of brain.*—1,055 grammes. Considerable wasting. Microscopic examination revealed characteristic changes of G. P. I. Large number of seizures before death.

*Cause of death.*—Exhaustion of seizures of general paralysis.

*Previous occupation.*—Laundress.

*Length of time in Asylum.*—Six years.

*Case 25.*—A. B., Claybury Asylum. 128.M./07. Male, age 30 years. Autopsy 28 hours after death.

*Weight of brain.*—1,275 grammes.

*Cause of death.*—Acute pulmonary tuberculosis.

*Previous occupation.*—Painter.

*Diagnosis of mental state.*—Melancholia. Probably congenital imbecile with epilepsy. Began to have epileptic fits at 14. Threatened to commit suicide.

*Length of time in Asylum.*—Five years six months.

*Case 26.*—I. E., Claybury Asylum. 7.F.07/2. Female, age 38. Autopsy 40 hours after death, body in cold chamber.

*Weight of brain.*—1,020 grammes. Some general wasting.

*Cause of death.*—Pulmonary tuberculosis.

*Diagnosis of mental state.*—Recurrent melancholia.

*Previous occupation.*—Hawker with her husband.

*Length of time in Asylum.*—Has been in asylum three times since 1894. Resident for eight years prior to death.

*Case 28.*—M. R., Horton Asylum. 4/1/08. Female, age 17 years. Autopsy five hours after death. (Brain sent to Claybury and placed in cold chamber. Forty hours elapsed before material was collected.)

*Weight of brain.*—1,075 grammes.

*Cause of death.*—Tubercular salpingitis. Tuberculosis of lungs, intestines and left elbow joint.

*Diagnosis of mental state.*—Dementia præcox (katatonic stupor).

*Previous occupation.*—General servant.

*Length of time in Asylum.*—Three months.

*Case 29.*—C. H., Bexley Asylum. 2/3/08. Male, age 23 years. Autopsy 26 hours after death.

*Weight of brain.*—1,165 grammes.

*Cause of death.*—Lobar pneumonia. No tubercle.

*Diagnosis of mental state.*—Dementia præcox.

*Previous occupation.*—Labourer. Reached only IVth Standard at age of 13.

*Length of time in Asylum.*—Four months, twenty days.

*Case 30.*—W. C., Rainhill Asylum, Liverpool. 2,471. M., June/07. Male, age 23 years. Autopsy 30 hours after death. Body not kept in cold chamber.

*Weight of brain.*—1,435 grammes. Some general wasting in pre-frontal region. Brain œdematous, considerable excess of fluid.

*Cause of death.*—Marasmus. No tubercle, lungs healthy.

*Diagnosis of mental state.*—Dementia præcox.

*Previous occupation.*—Packer in factory.

*Case 40.*—M. E. G., Claybury Asylum. 31.F./08. Female, age 47 years. Autopsy three hours after death.

*Weight of brain.*—955 grammes. R hemisphere 420 grammes, L hemisphere 360 grammes. The brain was extremely wasted and much congested, especially the L hemisphere, which was taken for analysis. Microscopical examination revealed the characteristic changes of general paralysis. Patient had seizures on and off since admission, more severe and frequent six months prior to death.

*Cause of death.*—Acute lobar pneumonia.

*Diagnosis of mental state.*—General paralysis of the insane.

*Previous occupation.*—Housewife. Married.

*Length of time in Asylum.*—Eight years.

*Case 41.*—M. D., Horton Asylum. 19/2/08. Female, age 28 years. Autopsy 18 hours after death.

*Cause of death.*—Tuberculosis of lungs and intestines.

*Weight of brain.*—1,095 grammes.

*Diagnosis of mental state.*—Dementia præcox.

*Previous occupation.*—Married. Housewife.

*Length of time in Asylum.*—Three years nine months.

*Case 42.*—C. O'C., Horton Asylum. 3/3/08. Female, age 27 years. Autopsy 13 hours after death.

*Weight of brain.*—1,190 grammes.

*Cause of death.*—Morbus cordis. Fatty degeneration. Bronchitis. No tubercle.

*Diagnosis of mental state.*—Dementia præcox.

*Previous occupation.*—Domestic servant. Single.

*Length of time in Asylum.*—Four years eleven months.

*Case 70.*—J. E. S., Department of Pathology, University of Chicago. 1/5/08. Male, age 43 years. Autopsy 4-5 hours after death.

*Weight of brain.*—1,400 grammes.

*Cause of death.*—Diffuse suppurative meningitis. (Duration of illness one week.)

*Mental state.*—Normal.

*Previous occupation.*—M.D. Surgeon.

#### SUMMARY.

Methods have been devised and are given in detail (1) for the estimation of the proximate constituents of the brain, and (2) for the estimation of the elements phosphorus and sulphur in the various groups of constituents: protein, lipoid, neutral and inorganic sulphur; protein, lipoid

and extractive phosphorus. Preliminary analyses have been made in a few cases on the grey and white matter separately. On account of the small quantities of the elements actually present in the brain, these analyses have only been regarded as of value when the analysis of a 100-gramme uniform sample of the whole brain yielded confirmatory results.

The methods have been employed for the analysis of 20 brains from normal and pathological cases, with the following results:—

(1) Analysis of the brain at different ages shows that with the growth of the brain there is a decrease in the amount of moisture, proteins, extractives and ash; and the cerebrins, lipoids and cholesterin increase. Also there is an increase in the lipid sulphur and phosphorus and a decrease in the neutral and inorganic sulphur and extractive phosphorus.

(2) Differences may be determined in the brains of different species, as demonstrated by a comparison of the human brain with that of the dog. This subject will be discussed by one of us (W. K.) at a later date.

(3) Comparison of brains from cases in which the causes of death were of an entirely different character showed no variations of importance. As the cause of death in one of these cases was "hæmorrhage due to erosion of peritonsillar abscess," it is apparent that the amount of blood present in the brain at death does not introduce any error of importance.

(4) Six brains from cases of dementia præcox have been examined, four by analysis of a uniform sample of the whole brain, and two by analysis of the grey and white matter separately. The results obtained on three cases already published (13) in which the analyses were made on the grey and white matter separately have been confirmed. Compared with the normal, the amount and distribution of phosphorus shows no marked change, but the neutral sulphur shows a great diminution while the inorganic and protein sulphur is relatively increased. Thus so far, nine cases in all have been examined and found to give results which, although varying among themselves, all tend in the same direction, *i.e.*, a *diminution of the neutral sulphur*. This variation appears to be independent of the cause of death and so far has not been found in other forms of insanity. It does not seem then unreasonable to suppose that the subjects of this mental disorder may possibly possess a general bodily inherent deficiency for oxidation processes. Examination of other tissues of the body for neutral sulphur and its proportion to the total sulphur contents would help materially to decide this point. In the meanwhile some support to this view of a general inherent bodily deficiency for oxidation processes is afforded by Pighini's observations on the increase of neutral sulphur in the urine in this disease.

(5) *Five brains* from cases of general paralysis have been examined, four by analysis of the brain as a whole and one by analysis of the white and grey matter separately. These cases were selected as controls of the analytical technique for the dementia præcox cases. *They do not show any marked change in the neutral sulphur content of the brain.* Compared with the normal, the results show that the destructive changes in this disease affect the brain generally and not one constituent in particular. There is, however, a tendency for the lipoid phosphorus to be decreased, indicating a greater destruction of the phosphatids.

The application of these methods to the study of other tissues seems quite promising, and will be taken up in the course of time in the laboratories from which these observations have been reported.

In conclusion, we would express our indebtedness to the Pathological Sub-Committee of the London County Council for the many facilities afforded to us, and to Dr. F. W. Mott, F.R.S., for his valuable suggestions from time to time, and aid in obtaining the large amount of varied material, without which the work could not have been done.

Also we would thank the many gentlemen to whom we are indebted for normal and pathological material and clinical histories. Dr. Geo. A. Watson and Dr. Wells have kindly aided us with material and histological reports. Mr. H. C. Corper has assisted us with some of the phosphorous estimations.

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## THE ORGANIC METABOLISM IN DEMENTIA PRÆCOX.

(Calorien, Albumin, N-total, Xanthin Bases, Uric Acid, Urea, S-acid, S-neutral.)

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## NOTE I.

Kraepelin was the first to consider dementia præcox as a morbid syndrome associated with profound, but indefinite, modifications of the organic metabolism. A large number of communications have appeared regarding the clinical symptoms of the disease, but very little has been done to discover the metabolic disturbances which accompany these symptoms, in a scientific manner following the work of Bischoff, Voit, Pflüger and Rubner.

In the metabolic experiments described in this communication I have followed the methods of the above-mentioned authors and have quantitatively estimated the metabolism of different food elements in my patients, making analyses of these substances when introduced in known quantity into the organism and of their products when excreted.

For the experiments I have used a diet comprising bread, milk, lean beef and eggs, in which the nitrogen, albumen, fat and carbohydrates were quantitatively estimated. The patients were kept in bed during the period of the experiment and watched in order that none of their food or excretions were lost. The nitrogen and fat were estimated in the fæces, desiccated after solution in water acidulated with sulphuric acid. The total nitrogen, urea, uretic nitrogen, xanthin bases, uric acid, total sulphur, and the acid and neutral sulphur were estimated in the urine. The number of heat calories acquired by the organism was calculated from the quantity of fat and albumen assimilated by means of the known factors of Rubner.

I chose for my experiments patients in the acute and advanced stages of the disease. The results obtained in the two types presented marked differences, as is shown by the following experiments on four chronic and two acute cases of dementia præcox.



## A.—DEMENTIA PRÆCOX. ADVANCED STAGE.

*Observation I.*—S.T. Age, 33 years. Duration of experiment, 7 days. Average daily yield of faeces, 30 grammes (desiccated), containing 2.15 grms. nitrogen and 6.188 grms. fat. The weight varied from 50.0 to 50.1 kilos, the temperature from 36° C to 36.4° C and the pulse from 100 to 105.

TABLE I.—Shewing average daily intake and output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in the food. g.	Albumen g.	Fat. g.	Carbo- hydrates. g.	Water. c.c.	Urine excreted. c.c.	N. in the Urine. g.	N. in the Faeces. g.	N. balance.	Albumen decomposed. g.	Per cent. of Albumen absorbed.
14.2	80.38	39.8	251	1330	711	10.54	2.15	+1.53	65.88	81.95

TABLE II.—Table of the Calories.

INTAKE.			DECOMPOSITION.		
Albumen ...	...	80.38 grammes = 329.6 calories.	65.88 grammes = 270.1 calories.		} Per cent. of calories utilized = 6.77.
Fat ...	...	39.8 " = 370.1 "	33.61 " = 312.6 "		
Carbo-hydrates ...	...	251 " = 1029.1 "	251 " = 1029.1 "		
Total ... = 1728.8 calories.			Total ... = 1611.8 calories.		

TABLE III.—Nitrogen, Urea and Sulphur.

Urine excreted, c.c.	N. in Food, g.	N. excreted in Urine, g.	Urea, g.	Per cent. of Uretic N, g.	H <sub>2</sub> SO <sub>4</sub> , g.	S—acid, g.	S—neutral g.	Total S, g.	Per cent. of Neutral S on S—total	N. : S.
911	14.22	10.54	20.98	93.03	2.6918	0.8852	0.1946	1.0798	18	9.76

*Observation II.—B.D.* Age, 23 years. Duration of experiment, 7 days. The temperature varied from 36° C. to 36.5° C. and the pulse from 95 to 100. The weight was 76.5 kilos at the beginning and 76.45 kilos at the end of the experiment. Average daily yield of faeces, 28 grms. (desiccated), containing 2.432 grms. nitrogen and 6.39 grms. fat.

TABLE IV.—Shewing the average daily intake and output of Nitrogen and Albumen.

INTAKE.					OUTPUT.				
N in the Food. g.	Albumen. g.	Fat. g.	Carbo- hydrates. g.	Water. cc.	Urine excreted cc.	N in the Urine. g.	N in the Faeces. g.	N Balance.	Per cent. of Albumen absorbed.
14.26	80.15	39.45	251	1330	958	11.08	2.43	+0.75	86.4

TABLE V.—Table of the Calories.

INTAKE.				DECOMPOSITION.			
Albumen ...	...	80.15 grms.	= 328.6 calories	69.25 grms.	= 283.9 calories.	} Per cent. of calories utilized = 6.03.	
Fat ...	...	39.45 "	= 368.9 "	33.06 "	= 307.4 "		
Carbo-hydrates ...	...	251 "	= 1029.1 "	251 "	= 1029.1 "		
Total ...			= 1724.6 calories.	Total ...	= 1620.4 calories.		

TABLE VI.—Nitrogen, Urea, Xanthin Bases, Uric Acid, Sulphur.

Urine excreted. c.c.	N in Food. g.	N excreted in Urine. g.	Urea. g.	Percent of Uretic N.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> . g.	S acid. g.	S-neutral. g.	S-total. g.	Percent of S-neutral on S-total.	N : S.
958	14.26	11.08	21.01	88.48	0.1133	0.60	2.4097	0.7876	0.1488	0.9364	15.88	12.04

*Observation III.*—(G. A., age 21 years. Duration of experiment, 9 days. The weight varied from 59.0 to 59.1 kilos, the temperature from 36° C. to 36.7° C., and the pulse from 105 to 115. Average daily yield of faeces, 30 grms. (desiccated), containing 1.59 grms. nitrogen and 5.09 grms. fat.

TABLE VII.—Showing the average daily Intake and Output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in Food. g.	Albumen. g.	Fat.	Carbo- hydrates. g.	Water. cc.	Urine excreted. cc.	N. in Urine. g.	N. in Faeces. g.	N. balance. g.	Albumen decomposed. g.	Per cent. of Albumen absorbed.
		g.								
14.45	81.21	40.30	251	1330	1167	11.87	1.59	+0.99	74.28	91.46

TABLE VIII.—Table of the Calories.

INTAKE.				DECOMPOSITION.			
Albumen ...	...	81.21 grms.	= 333.0 calories	74.28 grms.	= 304.5 calories	} Per cent. of calories utilized = 43.5.	
Fat ...	...	40.30 "	= 374.8 "	35.21 "	= 327.4 "		
Carbohydrates ...	...	251.0 "	= 1029.1 "	251.0 "	= 1029.1 "		
Total ... = 1736.9 calories				Total ... = 1661.0 calories.			

TABLE IX.—Nitrogen, Urea, Xanthin bases, Uric Acid, Sulphur.

Urine excreted. cc.	N. in food. g.	N. excreted in Urine. g.	Urea. g.	Per cent. of Uretic N.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> . g.	S. Acid. g.	S. neutral. g.	S. total. g.	Per cent. of S. neutral on S. total.	N. · S.
1167	14.45	11.87	22.5	88.44	0.1821	0.604	2.6043	0.855	0.1778	1.0317	17.25	11.32

TABLE X.—Showing the average daily Intake and Output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in Food. g.	Albumen, g.	Fat. g.	Carbo- hydrates, g.	Water. cc.	Urine excreted. cc.	N. in Urine. g.	N. in Fæca. g.	N. balance. g.	Albumen decomposed g.	Per cent. of Albumen absorbed.
14.45	81.4	40.3	251	1430	1350	12.14	1.586	+ 0.72	75.88	93.21

TABLE XI.—Table of the Calorien.

INTAKE.			DECOMPOSITION.			Per cent. of calories utilized
Albumen ...	81.4 grms.	= 333.7 calories	75.88 grms.	= 304.0 calories	}	
Fat ..	40.3 "	= 374.8 "	32.62 "	= 303.4 "		
Carbohydrates ...	261.9 "	= 1029.1 "	251.0 "	= 1029.1 "		
Total	...	1737.6 calories	Total	...	1636.5 calories	

TABLE XII.—Nitrogen, Urea, Xanthin bases, Uric Acid, Sulphur.

Urine excreted. cc.	N. in Food. g.	N. in the Urine. g.	Urea. g.	Per cent. of Ureic N.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> . g.	B. Acid g.	S. neutral g.	S. total. g.	Per cent. of S. neutral on S. total.	N. : S.
1350	14.45	12.14	22.25	85.3	0.1399	0.3374	3.24	1.0587	0.319	1.2347	22.95	9.75

## B.—DEMENTIA PRÆCOX. ACUTE STAGE.

(*Observation V*.—M. S. Age 22 years. This patient was examined in two successive periods. In the first stage he was in a state of katatonica alternated with fits of impulsiveness and motor restlessness. The weight varied from 62·3 to 62·0 kilos, the temperature from 36·9° C. to 37·1° C., and the pulse from 85 to 90. Period of experiment, 7 days. Average daily yield of faeces, 21 grms. (desiccated), containing 1·263 grms. nitrogen and 5·13 grms. fat.

TABLE XIII.—Showing the average daily intake and output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in Food. g.	Albumen. g.	Fat. g.	Carbo- hydrates. g.	Water. cc.	Urine excreted cc.	N. in Urine. g.	N. in Faeces. g.	N. balance. g.	Albumen decomposed g.	Albumen of the body destroyed. g.
14·58	82·2	41·07	251	1370	1365	17·17	1·26	—3·85	107·3	25·1

TABLE XIV.—Table of the Calorien.

INTAKE.			DECOMPOSITION.			
Albumen ...	...	82·2 grammes =	337·0 calories.	107·3 grms.	= 440·0 calories.	} Excess of calories supplied by the body = 55·2.
Fat ...	...	41·7 "	= 332·1 "	35·94 "	= 334·2 "	
Carbohydrates ...	...	251·0 "	= 1029·1 "	251·0 "	= 1029·1 "	
Total ...			= 1748·2 calories.	Total ...	= 1803·3 calories.	

TABLE XV.—Nitrogen, Urea, Xanthin bases, Uric Acid, Sulphur.

Urine excreted. cc.	N. in Food. g.	N. in Urine. g.	Urea. g.	Percent. of Ureic N.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> . g.	S. Acid. g.	S. neutral. g.	S. total. g.	Percent. of S. neutral on S. total	N. : S.
1365	14·58	17·17	29·19	79·32	0·229	1·13	3·4597	1·1312	0·3477	1·497	22·68	11·75

In the second period the katononia had ceased and the patient was more calm. Period of experiment, four days. Weight, 62 kilos. The temperature varied from 36° C. to 37° C., and the pulse from 80 to 84. Average daily yield of faeces, 20 grms. (desiccated), containing 0.82 grms. nitrogen and 3.16 grms. fat.

TABLE XVI.—Showing the average daily intake and output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in the Food. g.	Albumen. g.	Fat. g.	Carbo- hydrates, g.	Water. cc.	Urine excreted. cc.	N. in the Urine. g.	N. in the Faeces. g.	N. balance. g.	Albumen decomposed. g.	Albumen of the body decomposed. g.
14.55	81.98	40.78	251	1500	1450	15.06	0.82	-1.33	94.12	12.14

TABLE XVII. Table of the Calorien.

INTAKE.				DECOMPOSITION.	
Albumen ...	...	81.98 grammes.	= 336.1 calories.	94.12 grammes = 385.9 calories.	} The number of calories is in equilibrium.
Fat ...	...	40.78 "	= 379.3 "	37.62 " = 339.9 "	
Carbo-hydrates ...	...	251.0 "	= 1029.1 "	251.0 " = 1029.1 "	
Total...	...	1744.5 calories		Total ... = 1754.9 calories.	

TABLE XVIII.—Nitrogen, Urea, Xanthin Bases, Uric Acid, Sulphur.

Urine excreted. c.c.	N. in Food g.	N. in Urine. g.	Urea g.	Percent. Uretic N. g.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> g.	S. Acid. g.	S. neutral. g.	S. Total g.	Percent. neutral S. on total S.	S. : N.
1450	14.55	15.06	30.33	93.9	0.081	0.64	3.2984	1.0789	0.2421	1.321	18.33	11.4

*Observation VI.—F. E., aged 29 years. Duration of experiment 7 days. The temperature varied from 36.8° C. to 37.1° C., and the pulse from 80 to 85. Weight 64 kilos. Average daily yield of faeces 161 grms. (desiccated), containing 0.782 grms. nitrogen and 4.37 grms. fat.*

TABLE XIX.—Showing the average daily Intake and Output of Nitrogen and Albumen.

INTAKE.					OUTPUT.					
N. in the g. Food.	Albumen. g.	Fat. g.	Carbo- hydrates. g.	Water. g.	Urine excreted, cc.	N. in Urine. g.	N. in Faeces. g.	N. balance. g.	Albumen decomposed g.	Albumen of the body decomposed. g.
14.70	82.93	41.62	251	1330	1290	15.12	0.78	—1.2	99.5	11.57

TABLE XX.—Table of the Calories.

INTAKE.			DECOMPOSITION.		
Albumen ...	...	82.93 grms.	94.5 grms.	= 387.5 calories	} The number of calories is in equilibrium.
Fat ...	...	41.62 "	37.25 "	= 346.4 "	
Carbohydrates ...	...	251.0 "	251 "	= 1029.1 "	
Total ... 1764.0 calories			Total ...	1763.0 calories	

TABLE XXI.—Nitrogen, Urea, Xanthin Bases, Uric Acid, Sulphur.

Urine excreted c.c.	N. in Food. g.	N. in Urine. g.	Urea. g.	Per cent. of Uretic N.	Xanthin bases. g.	Uric Acid. g.	H <sub>2</sub> SO <sub>4</sub> . g.	S. Acid. g.	S. neutral g.	S. Total. g.	Per cent. Neutral S. on Total S.	N : S
1290	14.7	15.12	31.71	85.8	0.085	0.579	3.7585	1.194	0.2805	1.4759	19.10	10.65

The preceding tables show that two different alterations of the organic metabolism are present. In the acute stage of the disease the organism is subjected to a destruction of its own albumen as evidenced by the increased excretion of nitrogen and sulphur in the urine, and notwithstanding the fat lost in the fæces (24 to 27 per cent.) the heat used by the body is in excess of the supply. In the more advanced forms, however, the excretion of nitrogen in the urine is diminished, for a good part of the ingested nitrogen is lost in the fæces, so that only 80 to 90 per cent. of the albumen is absorbed. If we add to this the loss of fat in the fæces (varying between 20 to 25 per cent.), the assimilated calories become much less, and we may consider that 5 to 6 per cent. of the heat produced is not utilised.

In both phases of the disease the excretion of sulphur in proportion to nitrogen is increased and there is also an increased excretion of xanthin bases. These two facts might be associated with an abnormal destruction of the nucleo-proteid of the organism. Clinical examination of the abdomen failed to show alterations that would explain such anomalies of the metabolism. Therefore, lacking more exact knowledge, we are obliged to consider the change as being due to defective organic chemical metabolism. This change, since it cannot be ascribed to any external cause, may be considered as caused by an auto-intoxication. In the first stage of the disease, the organism is subjected to a toxic condition the cause and origin of which is unknown, and reacts to it by a destructive proteid metabolism and by an alteration of its physical functions. Certainly the toxin must be powerful, if gauged by the marked destructive reaction of the tissues and the profound alteration of the mental condition, which more or less rapidly progresses to dementia and from which recovery is very infrequent. In the first four cases observed the disease was rapidly progressive, and the dementia soon became pre-eminent above all other physical symptoms.

The fact that, in the advanced stages of the affection, the nitrogen and albumen either cease to be absorbed or to be excessively decomposed indicates either an inadequate assimilation by the intestinal tract or a cessation of the destructive organic metabolism. The heat metabolism is no longer increased. The quantity of nitrogen and urea and the oxidation of the sulphur as sulphurous acid are completely normal. The facts, excluding an alteration of the oxidising processes, lead us to the hypothesis that the intestinal and pancreatic juices, especially the latter, in these patients have a deficient action. I may add in support of this that there were muscle fibres and much fat in the fæces.



There are, however, two facts that still require explanation, and they are (1) the augmented excretion of sulphur in proportion to nitrogen of the urine, and (2) the increased excretion of xanthin bases. As shown by the tables, these changes are common to both phases of the disease, but are more apparent in the acute stage (Case V.). In both instances we must infer that the nucleo-proteids and sulphur-containing substances of the organism undergo a destructive metabolism, and conclude that in the more advanced period of the disease the auto-intoxication, though less marked than in the early stage, is still active in the organism, and in dementia præcox two types of an altered metabolism exist, one as the result of the preceding acute phase, the other as the result of the disease still continuing in a chronic form.

#### NOTE II.

(N, NaCl, Ca, P, K, S.)

In the preceding observations I have attempted to show that in dementia præcox, generally considered, two different modifications of an altered organic metabolism may be distinguished. In some cases of the acute disease, when the patients present symptoms of mental excitement, negativism, impulsiveness, etc., the organism is subjected to a marked destruction of its own proteid, which fact is evidenced by an excessive output of nitrogen and sulphur compared with the intake; while in the advanced phase of the disease, when dementia has developed and the early symptoms—apathy, katatonia, and stupor and stereotypy—have become permanent, a decreased assimilation and a lapse of the increased nitrogen excretion are observed to occur.

To further confirm these preliminary experiments, I have undertaken the investigation of the metabolism of the following inorganic elements—sodium chloride, chlorine, calcium, potassium, phosphorus and sulphur. The method adopted for each experiment was as follows:—The patient was kept in bed during the period of the experiment and carefully watched in order that none of the excretions were lost. A known quantity of food was given. The food consisted of milk, bread, lean beef, eggs, sugar, Marsala wine, coffee, table salt, and water, in which the various

elements were estimated several times. Table I. shows the percentage composition of the various diets.

TABLE I.

Food.			N.	NaCl.	Cl.	Ca.	P.	S.	K.
Milk	...	c.c. 100	0.529	0.26	0.1578	0.1419	0.0828	0.0335	0.1426
Bread	...	g. 100	2.07	0.4719	0.2865	0.0108	0.135	0.0807	0.0808
Beef	...	g. 100	3.168	0.1893	0.114	0.0151	0.3267	0.0268	0.355
Eggs	...	g. 100	2.087	0.213	0.1291	0.0558	0.154	0.0490	0.0738
Marsala Wine	...	c.c. 100	—	—	—	—	—	0.03	—
Coffee	...	c.c. 100	—	—	—	—	—	0.0372	—
Water	...	c.c. 100	—	—	—	0.01	—	0.0048	—

The urine was analysed every 24 hours (8 a.m.—8 a.m.), the fæces were weighed immediately after evacuation, and the weight and number of stools recorded. They were diluted and heated on a water bath, then dried to constant weight at 100° C., and finally triturated and analysed.

I have studied the metabolism of these inorganic constituents in six cases, two in the initial acute phase and four in the later chronic phase of the disease. The first two recorded show the more interesting results, which are as follows:—

## A.—ACUTE PHASE.

*Observation I.*—P. T., male, aged 20 years. Marked family history of insanity. Duration of disease two weeks. Acute mania, parasthesia, negativism, sitophobia, tics, dilated pupils, dermatographism.

Period of experiment, 7 days. Temperature varied from 36° C. to 37.7° C.

Weight—May 8th	...	52.4 kilos.	} Period of experiment.
" 15th	...	52.2 "	
" July 15th	...	60.4 "	

Six months later the mental condition of the patient changed to dementia.

The Tables II. and III. show the average daily Intake and Output of the various constituents in grammes.

TABLE II.

URINE.							FÆCES.						
Quantity. c.c.	Sp. Gr.	N.	NaCl.	Cl.	Ca.	S.	Dried Sub- stance.	H <sub>2</sub> O	N.	NaCl.	Cl.	Ca.	S.
1590	1.016	20.582	6.46	3.924	0.1418	1.3442	18	18	0.839	0.533	0.214	1.202	0.014

TABLE III.

INTAKE.—FOOD.					OUTPUT.—URINE AND FÆCES.					BALANCE.				
N.	NaCl.	Cl.	Ca.	P.	N.	NaCl.	Cl.	Ca.	S.	N.	NaCl.	Cl.	Ca.	S.
13.058	9.078	5.520	1.6262	1.399	21.451	6.813	4.138	1.3438	2.2102	-8.393	+2.265	+1.485	+0.282	-1.185

*Observation II.*—V. G. Male, aged 31 years. For ten years at intervals there have been periods of alteration in his habits and mental condition. For a month, after some years of relative good health an acute agitated phase with delusions of persecution, hallucinations, sitophobia, negativism, mannerisms, has persisted. The experiments, 7 days' duration, were made during this period.

Digestive organs normal; temperature varied from 36° C. to 37° C.

Weight:—23rd February ... 63.6 kilos. } Period of experiment.  
 2nd March ... 63.5 " }  
 25th July ... 64.4 " }

After the experiment the mental condition rapidly turned to dementia.

Tables IV. and V. show the average daily intake and output of the various constituents in grammes.

TABLE IV.

URINE.							FÆCES.								
Quantity.	Sp. Gr.	N.	NaCl.	Cl.	Ca.	P.	S.	Dry Substances.	H <sub>2</sub> O.	N.	NaCl.	Cl.	Ca.	P.	S.
802	1.031	15.427	8.389	5.09	0.1031	0.9439	1.2658	25.57	85	1.926	2.312	1.406	0.837	0.798	0.04

TABLE V.

INTAKE—Food.						OUTPUT—URINE AND FÆCES.						BALANCE.					
N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.
16.288	12.377	7.502	0.9268	1.4878	0.7322	17.353	10.701	6.501	0.945	1.741	1.305	-1.06	+1.676	+1.001	-0.018	-0.254	-0.572

These two cases presented the disease in an acute form. In the first case, now of five months' duration, the primary attack ran a rapid course to dementia, as evidenced by the demented habits of the patient after the lapse of the acute phenomena. The second case is one of ten years' duration, now suffering from an acute exacerbation. The period of experiment was during a time when the mental symptoms, having become most marked, were diminishing in severity. Both cases show the negative balance of nitrogen, phosphorus, and sulphur. In the first case the large loss *per diem* of 8.393 grms. nitrogen, 0.811 grms. phosphorus, and 1.185 grms. sulphur is sufficient to lead to the conclusion that a pathological metabolic change exists. Case II. also presents this change, but to a less degree. Figs. I. and II. show the relation of the nitrogen and phosphorus in the food administered to that in the excretions represented graphically, and illustrates the changes in the two cases better than comment.

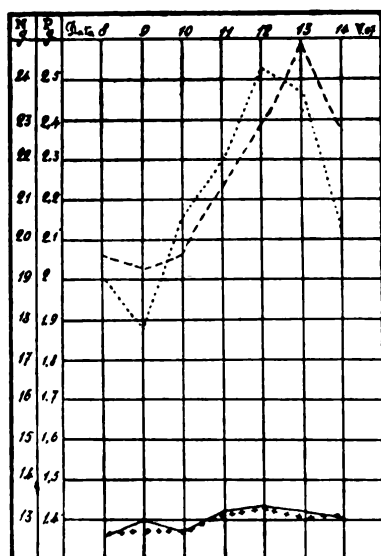


FIG. I.

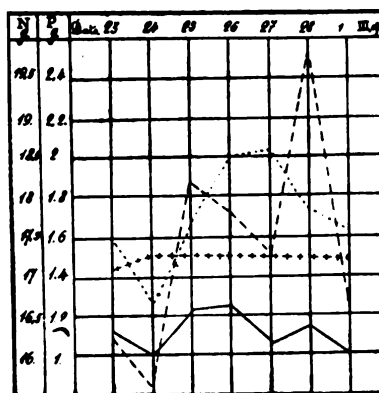


FIG. II.

— N intake (food).  
 + + + + P " "  
 - - - - N output (urine and faeces).  
 . . . . P " "

Table VI. shows the relation of the intake and output of the various elements under consideration for both cases, taking nitrogen as a constant = 100.

TABLE VI.

—	N.	Cl.	Ca.	P.	S.
<i>Observation I.—</i>					
Food ... ..	100	42.27	12.45	10.71	3.96
Urine and faeces ... ..	100	19.29	6.26	10.31	7.93
<i>Observation II.—</i>					
Food ... ..	100	46.06	5.69	9.13	4.49
Urine and faeces ... ..	100	37.46	5.44	10.03	7.52

It will be observed that the proportion of phosphorus to nitrogen in the excretions is equal or nearly equal to that in the food, while the proportion of chlorine and sulphur shows marked variations in the two series, the chlorine being diminished and the sulphur being increased.

The only element that maintains a relative equilibrium of balance is calcium, the results indicating that its metabolism is nearly normal and independent of the other salts. If we compare the excretions in the two cases we find corresponding figures except in the case of chlorine. The latter may be explained by the difference in quantity of NaCl administered and also by the slowness with which this compound reassumes the normal equilibrium.

The results in the case of nitrogen, calcium, phosphorus, and sulphur in both cases show an identical balance. The observations are too few to justify any conclusions correlating these variations with the clinical features of the disease, but it is evident from the above figures that the negative balance of N, P, and S is due in great part to a destruction of the phosphorised and sulphurised proteids of the organism.

## B.—CHRONIC CASES.

*Observation III.*—P. A. Male, aged 31 years. Duration of attack, two years. At the onset he was agitated, very confused, had hallucinations and sitophobia. For some time he was immovable and in a state of stupor, having copious salivation and intervals of violent impulsiveness. For a year he has been calm. Has a strange look, mannerisms, grimaces, and delusions. No abnormality of the internal viscera could be detected by clinical examination.

Duration of experiment, 7 days. Temperature varied from 36.2° C. to 36.5° C.

Weight:—17th January ... 54.5 kilos. } Period of experiment.  
 22nd January ... 54.5 " }  
 August ... 54.4 " }

Tables VII. and VIII. show the average daily intake and output of the various constituents in grammes.

TABLE VII.

URINE.								FÆCES.							
Quantity.	Sp. gr.	N.	NaCl.	Cl.	Ca.	P.	S.	Dry Sub-stance.	H <sub>2</sub> O.	N.	NaCl.	Cl.	Ca.	P.	S.
993	1.025	11.992	11.573	7.003	0.161	0.8241	1.0458	28	1.88	1.926	2.332	1.414	1.388	0.561	0.067

TABLE VIII.

INTAKE (Food).						OUTPUT (Urine and Faeces).						BALANCE.					
N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.
16.214	14.914	9.038	1.0597	1.4547	0.7712	13.918	13.738	8.317	1.549	1.385	1.1133	+2.292	+1.176	+0.721	-0.489	+0.069	-0.342

*Observation IV.*—R. G. Male, aged 30 years. For many years he has shown the same stereotyped condition of mental weakness and mutism. The pulse is frequent and feeble, and the hands are cyanotic. Durations of experiment, 8 days.

Temperature varied from 35.2° C. to 36.0° C.

Weight :—30th January, 1906 ... 50.25 kilos.  
3rd April, 1907 ... 49.2 " } Period of experiment.  
10th April, 1907 ... 49.2 "  
August ... 49.1 "

Tables IX. and X. show the average daily Intake and Output of the various constituents in grammes.

TABLE IX.

URINE.								FÆCES.							
Quantity.	Sp. Gr.	N.	NaCl.	Cl.	Ca.	P.	S.	Dry Sub- stances.	H. O.	N.	NaCl.	Cl.	Ca.	P.	S.
1060	1.023	13.757	9.485	5.748	0.2088	0.8059	1.3155	25	64	1.358	0.198	0.12	1.103	0.509	0.036

TABLE X.

INTAKE.—FOOD.						OUTPUT.—URINE AND FÆCES.						BALANCE.					
N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.
16.292	11.341	6.873	0.971	1.4599	0.7662	15.115	9.675	5.878	1.3118	1.3149	1.3515	+1.177	+1.666	+0.995	-0.3409	+0.145	-0.585



*Observation V.*—S. L. Male, aged 30 years. The disease began seven years ago with stereotypy, tics, labial tremors, copious salivation. In a short time the patient became katatonic and the mental condition changed to dementia. For four years the left arm has been contracted, the fore-arm flexed with clenching of the fist. The extremities present a certain waxy flexibility. Viscera normal.

Duration of experiment 5 days. Temperature varied from 36° C. to 36.5° C.

Weight:—23rd March, 07 ... 45.0 kilos } Period of experiment.  
27th March, 07 ... 45.1 „

Tables XI. and XII. show the average daily intake and output of the various constituents in grammes.

TABLE—XI.

Quantity. cc.	URINE.						FÆCES.					
	Sp. Gr.	N.	NaCl.	Cl.	Ca.	S.	Dried Sub- stance.	H <sub>2</sub> O.	N.	NaCl.	Cl.	S.
962	1.025	12.707	10.412	6.3255	0.3056	0.779	22.6	130	1.59.	0.56	0.338	0.015

TABLE—XII.

INTAKE.—FOOD.						OUTPUT.—URINE AND FÆCES.						BALANCE.					
N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.
15.736	11.283	6.859	0.9559	1.342	0.7092	14.297	10.972	6.663	0.9484	1.107	1.175	+1.439	+0.311	+0.196	+0.007	+0.233	-0.465

*Observation VI*.—A. G. Male, aged 24 years. Admitted to Saargemund Asylum two years ago and presented phases of excitement and depression, with marked suicidal tendencies. Some months before he was in a condition of katatonic stupor. At present he is in the acute stage, but calm.

Duration of experiment, 7 days. Temperature varied from 36.2° C. to 36.7° C.

Weight :—April 12th ... 59.6 kilos. } Period of experiment.  
April 19th ... 59.7 " }

Tables XIII. and XIV. show the average daily intake and output of the various constituents in grammes.

TABLE XIII.

URINE.								FÆCES.							
Quantity. cc.	Sp. gr.	N.	NaCl	Cl.	Ca.	P.	S.	Dry sub- stance.	H <sub>2</sub> O. cc.	N.	NaCl.	Cl.	Ca.	P.	S.
1384	1.022	12.80	12.556	7.609	0.5642	0.8085	1.2057	21	35	1.59	0.209	0.1288	0.749	0.479	0.0776

TABLE XIV.

INTAKE (Food).					OUTPUT (Urine and Faeces).					BALANCE.							
N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.	N.	NaCl.	Cl.	Ca.	P.	S.
16.088	13.319	8.072	0.9654	1.429	0.7617	14.39	12.765	7.735	1.3132	1.2875	1.2823	+1.698	+0.554	+0.337	+0.347	+0.141	-0.520

In the last four cases described the disease had become chronic, and dementia was present. Outbreaks of excitement had ceased, although the other symptoms, hallucinations, mannerisms, katatonia, negativism, echolalia, etc., forming the clinical picture of the disease, which had remained unchanged for many years, still persisted. This chronic phase is well distinguished clinically from the acute phase, and is characterised by a special metabolism of its own.

In the four cases examined there is a loss of calcium and sulphur. The results also show a retention of chlorine, but this is slowly returning to the normal equilibrium.

Figs. III., IV., V., and VI. represent the balance of nitrogen and phosphorus in the four observations expressed graphically.

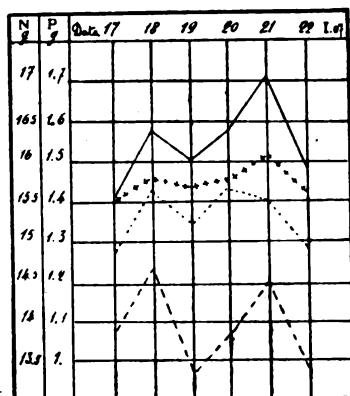


FIG. III.

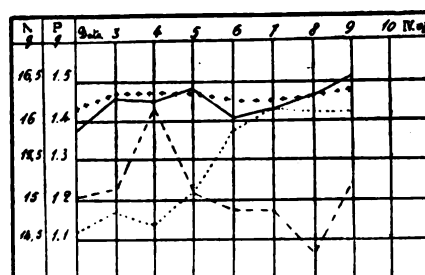


FIG. IV.

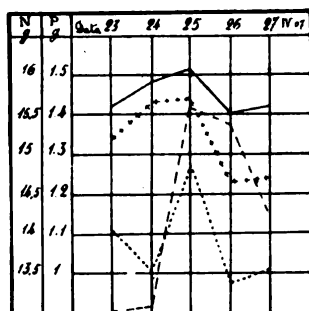


FIG. V.

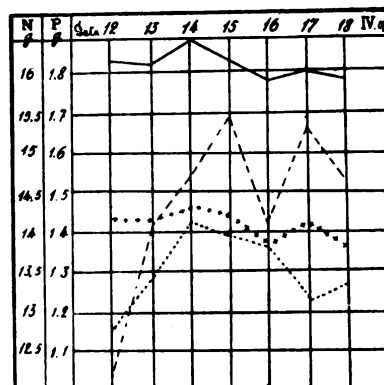


FIG. VI.

— N intake (food).  
 + + + + P " "  
 - - - - N output (urine and faeces).  
 . . . . P " "

It will be observed that the lines of the elements when introduced into and when excreted from the organism run practically a parallel course, which is not the case in Figs. I. and II. (acute cases).

Table XV. shows the relation of the intake and output of the various elements under consideration, taking nitrogen as a constant = 100.

TABLE XV.

—	N.	Cl.	Ca.	P.	S.
<i>Observation III.—</i>					
Food ... ..	100	55.74	6.53	8.97	4.14
Urine and faeces ... ..	100	59.75	11.13	9.95	8.58
<i>Observation IV.—</i>					
Food ... ..	100	42.19	5.96	8.96	4.70
Urine and faeces ... ..	100	38.89	8.68	8.70	8.94
<i>Observation V.—</i>					
Food ... ..	100	43.59	6.07	8.53	4.50
Urine and faeces ... ..	100	46.61	[6.63]	7.74	8.21
<i>Observation VI.—</i>					
Food ... ..	100	50.17	6.00	8.88	4.73
Urine and faeces ... ..	100	53.75	9.13	8.94	8.91

The results show that the proportion of phosphorus to nitrogen in the excretions is the same as that in the food, therefore we may conclude that the retention has been in the same proportion. The proportion of chlorine to nitrogen is also the same in the two series. The sulphur and calcium, however, in proportion to the other elements in the series, are in great excess in the excretions.

The excess of calcium is variable, but the sulphur in all four cases maintains a proportionately high figure. The proportion of N:P:S is practically the same in the four cases. It would seem then that the metabolism of these patients is characterised by a proportional retention of nitrogen and phosphorus; by a proportional loss of sulphur and by an independent varying loss of calcium.

It is also necessary to state that the water metabolism is changed. With difficulty the four patients were induced to swallow 300 to 400 cc. of water which was added to their daily food. It was estimated that the food *per diem* contained about 1,200 cc. of water, thus every patient took daily from 1,500 to 1,600 cc. and excreted in the urine and faeces 1,000

to 1,400 cc. The researches of Pettenkofer and Voit\* show that the moisture perspired by the skin and lungs by a normal man in a state of rest oscillates from 680 to 1,200 cc. in 24 hours, 60 per cent. passing through the skin. Comparison with these figures shows that none of the patients attained the lowest limit of moisture excreted by the lungs and skin, the difference between the intake and output of water (urine and fæces) being 300 to 500 cc. The excretion of moisture by the skin and lung is therefore much diminished, and this would explain the relaxed metabolism of the nitrogen and sulphur, and the imperfect heat metabolism—the sub-normal temperature, etc., which are characteristic of these patients. However, the organism may have contributed to the excess of water in the urine and fæces.

This series of observations, although special attention has been paid to the metabolism of the inorganic elements, leads to the same conclusions as the first series in which the organic metabolism (N—total, urea, uric acid, xanthin bases, sulphuric acid, neutral S and total S) was investigated, and in the two clinical syndromes of dementia præcox examined, two different modifications of an altered metabolism are apparent. I may mention that the patients subjected to the experiments were chosen as typical examples of the two phases. In the varied and numerous cases of dementia præcox, probably there are many that present a normal metabolism, and *a priori* it is probable that between the period of remission or recovery from the acute phenomena and the varied symptomatology (also present in the chronic phase) that characterise the disease, the metabolism of the subjects should have returned to within physiological limits. To control these researches I subjected two cases of dementia in perfect health to the same experiments. The metabolism in these cases appeared to be absolutely normal except for a slight diminution in the absorption of nitrogen and phosphorus.

Thus in all 12 cases, four in the acute stage and eight in the chronic stage of dementia præcox, have been examined and have shown two characteristic modifications of an altered metabolism corresponding with the clinical syndromes.

The negative balance of nitrogen, phosphorus and sulphur, the excessive excretion of urea, uric acid and xanthin bases, with an accompanying progressive decrease in weight, indicates that the phosphorised and sulphurised proteids of the organism have undergone destruction. The temperature rises slightly, 37° C. to 37.7° C., but this slight increase could not account for this proteid destruction, for the observations of Linser and

\* PETTENKOFER and VOIT. Untersuchungen über den Stoffverbrauch des normalen Menschen. *Zeitschrift für Biologie* II. 459. 1866.

Schmid show that a body temperature of at least 40° C. is necessary to cause a dissolution of the proteids.

In the advanced phase the proportional retention of nitrogen and phosphorus (as compared with the acute stage) indicates a decreased metabolism, but in spite of this retention the weight of the patients fluctuates and often decreases. This fact may be explained, for while nitrogen and phosphorus are being retained in the organism there is an excessive excretion of calcium and sulphur. Moreover, it may be possible that the excess of moisture excreted in the urine may influence the body weight.

It is evident that in the urine of these cases there is an excess of sulphur which cannot have been derived from the food administered, and which must have resulted from the decomposition of some sulphurised proteid. It is interesting to mention here that Koch,\* at the suggestion of Mott, submitted several brains of dementia præcox to chemical analysis and compared them with the normal brain. He found a marked diminution of the neutral sulphur ("taurin-like sulphur") and an increase of the inorganic sulphates. These results have been confirmed by Koch and Mann (*vide* p. 217), who have found that this variation does not exist in other forms of insanity, *e.g.*, general paralysis, melancholia.

The results show an increased excretion of calcium except in the fifth case, in which the analyses were incomplete. The excess reached as much as 58·4 per cent. over the intake (normal 5 to 10 per cent.), and appeared to be most marked in cases with stupor of the katatonic form.

#### SUMMARY.

With a view of throwing light on the metabolic changes associated with the profound symptoms of dementia præcox, I have selected four typical cases of the disease in the acute and eight in the more advanced stage, and in them I have studied the metabolism of the various food elements by means of numerous analyses of the food administered and the excretions. Each case gave results of interest, which may be summarised as follows:

(1) In the dementia præcox of Kraepelin, the acute phase and the advanced phase each present different modifications of a latered metabolism.

\* Koch, W. Zeitschrift, für Physiologische Chemie, 1907, liii., p. 496.

(2) In the acute phase, as evidenced by motor restlessness, sitophobia, violent impulsiveness, slight elevation of temperature, etc., there is a negative balance of nitrogen (urea, uric acid, xanthin bases) and of phosphorus and sulphur, indicative of a marked dissolution of the phosphorised and sulphurised proteids of the organism.

(3) In the advanced phase, as evidenced by dementia, negativism, tics, grimaces, katatonia, etc., there is a proportionate retention of nitrogen and phosphorus, a loss of sulphur proportionate to these elements, and an independent loss of calcium.

(4) In the two phases investigated there is an altered water metabolism, and a relaxed excretion of chlorine.

## A BACTERIOLOGICAL EXAMINATION OF THE CEREBRO- SPINAL FLUID IN DEMENTIA PRÆCOX.

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Acting on the suggestion and advice of Dr. Mott we have investigated the cerebrospinal fluid withdrawn by lumbar puncture during life from cases of dementia præcox under treatment in the London County Asylum at Claybury, paying special regard to the following points:—

1. The presence of micro-organisms.
2. The presence of protein, as evidenced by the Noguchi test.
3. The presence of cells in the deposit of the centrifuged cerebrospinal fluid.

*Technique.*—The difficulties that confronted us were (*a*) the possibility of air and skin contamination, and (*b*) the possibility of rendering the cerebrospinal fluid sterile by the introduction of antiseptics. Our first few experiments clearly demonstrated the great precautions necessary to avoid air contamination. Dr. Candler, in his somewhat similar work on general paralysis, has drawn attention to this source of error (*vide* p. 145), and we have been able to confirm his observations by exposing sterile culture plates to the air of the ward during the operation of lumbar puncture; in several instances a luxuriant growth resulted. In several cases also, before the skin was sterilized, we inoculated culture tubes with scrapings taken with a sterile knife from the patient's back near the point of puncture; in many cases we obtained a growth of a coccus.

The method of procedure in the first five cases was as follows:—The skin was cleansed with 1 in 200 carbolic solution, with subsequent applications of turpentine and ether, and finally with 1 in 200 carbolic lotion again. About 10 cc. of the fluid was withdrawn into a carefully sterilized centrifuge tube, and the fluid was pipetted off into the following media: broth, blood serum, slope agar, and, for the purpose of detecting any anaerobic organisms, glucose formate tubes were also employed. The Noguchi test was made on 1 cc. of the fluid, and the remainder was centrifuged and the deposit examined for cells.



In spite of the precautions taken the first five cases showed growths in three instances, the result of external contamination.

Cases 1 and 2 were sterile.

Case 3 showed a cloudiness in the broth culture after 24 hours' growth, which on examination in hanging drop preparation was found to be a non-motile organism, and on subculture proved to be the *Bacillus Subtilis*. After centrifuging, the supernatant fluid of this case was incubated for 24 hours; it contained several organisms, including the streptococcus and sarcinae.

Case 4 showed the presence of sporing organisms resembling sarcinae in the agar and glucose formate cultures at the end of 24 hours, otherwise the results were negative.

Case 5 showed a staphylococcus in the broth culture after subcultivation on agar. The other tubes remained sterile. From the number of diverse organisms which had been discovered we concluded that there must be some fault in our technique. The frequent presence of an organism resembling a mould convinced us that our precautions against air contamination had not been sufficiently stringent. In the next two cases therefore, instead of collecting the fluid into a centrifuge tube and later pipetting it off into the different media, we allowed the fluid to run directly from the needle into the culture tubes. These two cases showed a growth of streptococcus in both instances. The type of organism forced us to the conclusion that the infection was from the skin. We therefore substituted mercuric chloride solution for the carbolic lotion in our technique. In the next four cases cultures of the cerebrospinal fluid remained sterile. We recognised the possibility of the mercuric chloride being carried in with the needle and thus causing a fallacy in our results. To avoid this, after the skin had been cleansed as above, we further removed all traces of antiseptic by the repeated application of sterile distilled water.

Adopting this procedure, we examined 19 further cases, and in every instance obtained a *negative* result.

Noguchi has described the following method for detecting protein in the cerebrospinal fluid. One part of the cerebrospinal fluid is boiled for a short time with five parts of a 10 per cent. solution of butyric acid; one part of normal sodium hydrate solution is then added, and the mixture again boiled. If the tube is allowed to stand for 30 minutes to three hours, a coarse granular or flocculent precipitate denotes the presence of a protein, which Noguchi regards as pathognomonic of parasymphilitic affections. The presence of blood contamination renders the test valueless. None of the 30 cases of dementia præcox in which the fluid was free from blood gave the test.

*Conclusions.*—We have examined the cerebrospinal fluid withdrawn by lumbar puncture during life in 30 cases of dementia præcox and obtained a negative result in 23 cases after we had improved our technique. We are therefore forced to the conclusion that the reported discovery of any organism in the cerebrospinal fluid in dementia præcox should be regarded with great caution, and in the light of the difficulties we have encountered, we would suggest that any such organism may be the result of external contamination.

As one would expect the Noguchi test for proteins yielded a negative result in all fluids examined that were free from blood, and the examination for cells in the centrifuged deposit of the fluid was also negative.

We would express our gratitude to the Pathological Sub-Committee of the London County Council for the facilities afforded to us in proceeding with this work in the Laboratory, to Dr. Robert Jones, for the kindly interest he has taken in our endeavours; to Dr. Candler, whose previous experience with similar work has enabled him to aid us with much valuable advice; and to Mr. S. A. Mann for his constant kindness and assistance.

NOTES AND OBSERVATIONS ON FORTY CASES OF NEW  
GROWTH, INCLUDING EIGHTEEN INTRACRANIAL TUMOURS.\*

Examined in the Pathological Laboratory of the London County Asylums,  
Claybury,

BY HELEN G. STEWART, M.D.

IN the following paper the notes are given of 40 cases of tumour, examined consecutively in the laboratory of the London County Asylums at Claybury. Permission to work in the laboratory was kindly accorded by the Asylum Committee, for which privilege I am much indebted. Through the kindness of the Director, Dr. Mott, who placed at my disposal the cases of cerebral tumour which were sent to the laboratory for examination from all the London County Asylums (also a case under his care in Charing Cross Hospital, and one case of tubercular disease of the brain from the Children's Hospital in Great Ormond Street), I have had the opportunity of examining 18 cases of cerebral tumour, and, in addition, 22 cases of new growth of other organs occurring among the patients at Claybury Asylum. Of the latter, 21 were from *post-mortem* material, and one a breast which was amputated. The nature and position of the growths were as follows:—

- |                                            |   |                       |
|--------------------------------------------|---|-----------------------|
| 4. Gliomata                                | } | Intracranial Growths. |
| 2. Sarcomata                               |   |                       |
| 5. Endotheliomata                          |   |                       |
| 2. Adenomata                               |   |                       |
| 3. Syphilitic                              |   |                       |
| 1. Tubercular                              |   |                       |
| 1. Cancer                                  |   |                       |
| 6 Cases of cancer of the stomach.          |   |                       |
| 4 Cases of cancer of the breast.           |   |                       |
| 2 Cases of papilloma of bladder.           |   |                       |
| 1 Case of cancer of the lungs.             |   |                       |
| 1 Case of cancer of the intestine.         |   |                       |
| 1 Case of cancer of the bladder.           |   |                       |
| 1 Case of cancer of the suprarenal gland.  |   |                       |
| 1 Case of adenoma of the suprarenal gland. |   |                       |
| 1 Case of adenoma of the thyroid gland.    |   |                       |
| 1 Case of adenoma of the kidney.           |   |                       |
| 1 Case of adenoma of the prostate.         |   |                       |
| 1 Case of fibroma of the ovary.            |   |                       |
| 1 Case of cancer of the uterus.            |   |                       |

\* Being part of a Thesis presented for the M.D. degree of the Birmingham University,  
June, 1908.

The investigation was suggested by the discovery of cell inclusion, somewhat similar to those met with in cancer in the tissues of animals and human beings suffering from trypanosome infections. These cell inclusions were seen in the glands of dogs who had been inoculated with the *Trypanosoma equiperdum*, and in the brain and glands in cases of sleeping sickness. The tissue in which they were demonstrated was fixed in Müller's fluid, mordanted in an aqueous solution of iodine in potassium iodide, and stained from 5 to 12 hours in a 10 per cent. solution of Giemsa's stain at a temperature of 37°C.

When sections of cancer tissue were stained by this method, after fixing either in Müller's fluid or in Formalin in normal salt solution, it was found that the so-called "inclusions" were differentiated from the cancer tissue cells, and thus their form and distribution could be more easily studied.

Many other methods were also employed in studying these growths. Hanging drop specimens were made in many instances, and watched on the warm stage. Film preparations were made stained by numerous methods, but the best results for studying the inclusions were obtained by a modification of the "wet" method of film fixation. Thin films were exposed for about 30 seconds to the emanations from Thorium Nitrate, then mordanted in iodine solution and stained by Giemsa's fluid (50 per cent. in warm aq. dest. for 10 to 20 minutes).

By this means the atypical pink cells were first seen in the film preparations of a gliomatous tumour.

Zenker's and Fleming's methods of fixation have also been used for tissues in bulk, and acetic acid and alcohol, but with less good results. Sections have been stained by all the usual methods, including polychrome methylene blue, Heidenhain's method for glia tissue, etc.

The chief points which it has been my endeavour to investigate in the present research are:—

(1.) *The origin and method of spread of the growth.*—Under this heading the result of my examination supports the view that some tumours at any rate do not originate in a single cell or group of cells. Evidence of this was first noticed in gliomata, where a diffuse tendency to multiplication can be seen in the neuroglia cells over large areas.

(2.) *The origin and distribution of certain atypical cells.*—These cells, which have been described by many authors, were investigated by the modification of the Giemsa method mentioned above (which for brevity will, in future, be designated the I. G. method). It is held that these cells have a wide distribution, that they occur on the surface of the epithelium in both early and advanced cases of cancer of the alimentary tract; also free in the lymphatic vessels and spaces around the vessels

in gliomata, and may be seen invading the tissues in secondary growths without the intervention of the cancer cell proper.

It is suggested that these cells, whatever their origin and nature may be, are taken up by the epithelial cells as foreign bodies, and in this way engender the infiltrating habit of the malignant tissues.

(3.) *The cell reaction and changes.*—The lymphocytic infiltration in cancer has for long been recognised to be irregular in distribution. It has recently been contended that this small round cell reaction is due to mechanical irritation, and, therefore, it has seemed worth while to note that in these growths (especially noticeable in those of the brain), the lymphocytic infiltration appears to be perivascular, and not confined to, or necessarily connected with, those vessels which are distended by, or infiltrated with tumour growth.

*Case 1.—Glioma of the frontal region of the left Cerebral Hemisphere.*

J. C., aged 70, on admission had defective memory and hallucinations; later developed a tottering gait and some paralysis of the right side; became demented and died in a seizure.

*Post mortem.*—There was some atheroma of vessels and cardiac valves. The dura mater was adherent to the calvarium; the pia mater was thickened and there was some excess of cerebrospinal fluid. The whole of the anterior portion of the left cerebral hemisphere was occupied by a circumscribed mass, reaching from the anterior pole to the genu of the corpus callosum. It was yellow in colour but contained red areas suggesting hæmorrhage, and some parts of the periphery presented the appearance of yellow softening. The condition suggested some form of neoplasm which was undergoing a regressive metamorphosis. At about the middle of the central sulcus of the right Island of Reil was a definitely circumscribed pigmented spot about 5 mm. in diameter.

*Microscopic examination.*—Sections taken from the edge of the tumour showed degenerating tissue, in some places continuous with proliferating glia cells, in others cut off by fibrous strands.

The normal structure of cortex and medulla was replaced by proliferating glia tissue, and this was thickest and most cellular near the degenerating areas. The vessel walls were thickened and those within the growth were surrounded by dense fibrous tissue. Many of the vessels were thrombosed and some organised. There were numerous hæmorrhages and in some parts a well-marked lymphocytic infiltration. In sections stained by the I. G. method some cells, with protoplasm taking a clear pink stain and with dark almost black nuclei, were seen among the proliferating tissue around the vessels. The cortical nerve cells were disorganised and undergoing phagocytosis near the growth. The glia tissue showed proliferation for some distance away from the tumour area proper; it was well marked in the cortex of the upper part of the cerebral convolutions, less so at the lower end of the F. of Rolando, but could be traced as far as the left anterior calcarine region. No proliferation could be distinguished in sections from any portion of the right hemisphere. Scattered throughout the sections of all portions of the cortex of the

left hemisphere, but most marked at the periphery of the cortex of the Island of Reil were curious bodies which when small appeared within the protoplasm of glia cells and when large were lying free in the cortex. The smaller bodies were homogeneous, almost hyaline, and stained pale blue with the I. G. stain, and pink with Van Gieson's solution. The larger bodies stained pink at the periphery, and diffusely blue or violet internally with a double stain. Heidenhain's hæmotoxyl stained the centre a brownish black in some cases. These bodies gave the violet blue reaction of chitin when treated with iodine solution and zinc chloride and stained green by Bethe's method of staining chitin. They were dissolved by strong acids and acidified chloroform, leaving spaces in the tissue. The membranes over the growth showed fibrous thickening, endothelial cell proliferation, and marked small round cell infiltration around some of the vessels. In pieces of membrane taken from the central and occipital regions of the right hemisphere there was also a marked small round cell infiltration in some parts, but the membrane was not much thickened.

*Case 2.—Small round cell Sarcoma of the frontal lobe of the right Cerebral Hemisphere.*

J. L., aged 45, had a history of intemperance, sleepiness and dulness. He was depressed, demented, blind and tremulous. Knee jerks very brisk. Death occurred two months after admission from atony and distension of the bowel.

At the *post-mortem* examination there was found to be a general distension of the gut, especially marked in the large intestine without any sign of obstruction (? paralytic). On removing the calvarium there was seen to be some excess of cerebrospinal fluid, and much thickening and congestion of the pia arachnoid membrane. In the right hemisphere a large mass of new growth occupied the prefrontal region and extended into the inferior frontal convolution, where it presented a fungating appearance with pigmented areas. On section of the hemisphere the growth was seen to extend backwards as far as the middle of the lateral ventricle, but posteriorly only involved the white matter; at the level of the internal capsule there had been a definite hæmorrhage.

Microscopical examination of the growth showed small round cells, uniform in size, and staining reaction, which were divided in places by thin strands of fibrous tissue. There were numerous imperfectly formed blood vessels and evidence of hæmorrhage in the form of red cells and clot. At the margin of the growth areas of proliferating neuroglia cells were seen with branching processes, and there was well-marked proliferation of the endothelial cells lining the perivascular lymphatics.

The nerve cells of the cortex showed some disorganisation well beyond the edge of the growth. Chromatolysis and eccentricity of the nucleus were present in the central region, but the changes became less marked the farther the sections were taken from the vicinity of the growth, those from the parietal region being very little removed from the normal. Some of the vessels showed groups of lymphocytes around the walls, and these cells were also scattered throughout the white matter near to the growth. There was some proliferation of the perivascular endothelium in the cortex of the central region and numerous plasma cells were seen. In pieces of membrane taken from over the region of the growth there was patchy thickening due to overgrowth of the cells of the endothelial lining. Many of the vessels were surrounded by a well marked small round cell infiltration. In the membrane from the occipital region similar changes were present, but in a much smaller degree.

*Case 3.—Glioma of the frontal lobe of the left Cerebral Hemisphere.*

E. H., aged 45, had been weak-minded from childhood.

There was a history of fits and strangeness of manner for six months. He was dull, slow, stupid, and of faulty habits, had glycosuria, and died comatose.

At the *post-mortem* examination a large soft tumour occupied the left frontal region. It caused bulging of the lateral surface, and on the mesial surface had obviously pressed on the opposite hemisphere. The tumour extended through the left optic thalamus and pons, and in these regions contained hemorrhages. The cortex over the tumour areas was pale, and the striation indistinct. Films made from the growth, fixed by exposure to thorium nitrate and stained by the I. G. method, showed elongated cells with large nuclei and often branching processes. Scattered among these were irregularly round cells with dark nuclei and protoplasm staining a clear pink. These cells had generally rather a large amount of protoplasm in proportion to the size of the nucleus and did not resemble either the plasma cells or neuroglia cells in size, shape or colouring. Sections of the growth showed a uniform structure of neuroglial tissue. It was most cellular around the vessels, where there was often also an overgrowth of true fibrous tissue. There were numerous degenerated areas, mostly small, and at the edges of these and scattered throughout the tissue were numerous pink cells with dark nuclei. In some cases these pink cells were seen surrounding the vessels and replacing the neuroglial cells. The way in which this growth infiltrates the nervous tissue around, and the apparent method of extension by multiplication of the existing neuroglial cells some distance beyond the obvious edge of the tumour, resembles that described in Case 1. The membranes also were affected in a similar fashion to the other case, but the membrane over the lateral surface of the hemisphere in this case showed more small round cell infiltration around the vessel than was seen in any other case so far away from the centre of the growth.

*Case 4.—Glioma of the right Temporal Lobe.*

B. B., aged 67, had a history of having had a fit, but was only under supervision for one week. Death occurred from pneumonia with terminal gangrene.

At the *post mortem* there was seen to be a slight thickening of the pia mater and slight excess of cerebrospinal fluid. On dividing the cerebral hemispheres a circular, dark red, hæmorrhagic mass was seen (about 2 cm. in diameter) at about the centre of the right hippocampal gyrus. The whole of this gyrus and the adjacent temporal convolutions were abnormally soft to the touch, had some obliteration of their secondary sulci, and on section showed hæmorrhagic points. The differentiation of grey from white matter was not clear and the circular hæmorrhagic area only extended for about 5 mm. below the surface. Films of this region showed uniform glia cells with well-marked branching processes and numerous blood vessels. Sections of tissue taken from the same part showed distended, imperfectly formed vessels with numerous hæmorrhages. There was marked enlargement and proliferation of the endothelial cells and some lymphocytic infiltration in the vessels and tissues around. Some multi-nucleated cells were seen in the hæmorrhagic areas. The substance of the tumour consisted of a uniform growth of neuroglia cells with oval nuclei and branching processes, and the structure approached a cellular rather than a fibrous glioma. Very few nerve cells could be seen in the cortex over the growth and most of those present were in process of disintegration. Sections

taken from the anterior end of the hippocampal gyrus showed also a uniform structure of glia cells with well-marked perivascular lymphocytic infiltration, which extended some distance into the tissues around the vessels and was not confined to the perivascular lymphatics. Many of the glia cells in this case contained hyaline bodies similar to those described in Case 1. They could be seen in the substance of the glia cells as small, round, almost transparent globules, and all sizes could be traced to the larger free bodies taking an acid stain at the periphery and basic in the centre. In some cases the rim of the latter appeared to be separated from the centre and had a lobulated, mulberry-like appearance. The membranes over the growth showed an increase of endothelial cells and a lymphocytic infiltration around the vessels. In the membranes from other regions there was a general thickening and increase of endothelial cells, but much less lymphocytic infiltration around the vessels.

*Case 5.—Glioma of left Frontal Lobe.*

G. C., aged 54 years, commenced to have epileptic fits 12 years before admission, and these had continued with varying intensity ever since. On admission the speech was coherent, and the attention easily obtained and retained, and the patient was clean, decent and quiet. The memory was bad, the patient was dull and depressed, and had both illusions and delusions. Hearing was defective, and two months before death there began to be some difficulty in speaking. Death in status epilepticus.

At the *post-mortem* examination there was seen to be a tumour of the left frontal lobe of the brain, beginning about 1.5 cm. from the anterior pole of the hemisphere and extending backwards about 6 cm.; in width the tumour area measured 4.5 cm. The colour of the growth was a pinkish grey, and the change to normal tissue on the anterior and inner surfaces was imperceptible, but on the lateral surface (Island of Reil) there was a distinct line of demarcation apparently fibrous in nature, limiting the growth. Microscopical sections of the growth showed a uniform overgrowth of glial tissue with strands of cells running through it in places. These cells were for the most part oval or round, and mononuclear, and had no definite relation to vessels. All stages could be seen from round cells to typical branched neuroglial cells. Sections taken from the cortex beyond the part affected by the tumour to the naked eye showed a great increase of glial nuclei, decreasing in degree as the tissue was farther removed from the growth, suggesting rather that the overgrowth of glia was due to a chronic proliferative influence spreading over the region, than that it was a localised growth extending into the brain tissue.

The nerve cells showed deviation from their normal character in proportion to their implication in the growth. The remains of a few were found within the growth, at the edge they appeared in various stages of disintegration, and in many cases were seen as mere uniformly staining, elongated masses of protoplasm.

The vessels of the cortex showed an undoubted proliferation of endo- and perithelium, but not to a very marked extent.

The membranes over the growth showed a patchy endothelial proliferation, and in some places a moderate degree of infiltration around the vessels. In the membranes over the occipital region these changes were also present, but less marked than in the membrane near the growth.



*Case 6.—Adenoma of the Pineal Gland.*

J. W., aged 48. On admission was dull, stuporose, incoherent, and depressed.

The motor power was impaired in both legs and the right arm, and the patient was unable to stand alone. The speech was thick and slurred, the knee jerks brisk; there was no ankle clonus and no nystagmus or ptosis. The pupils were equal, regular, and reacted to accommodation, although there was marked optic neuritis. In the asylum the patient had frequent attacks of tachycardia without discernible cause. Between the attacks she was either stuporose or restless and excited.

At the *post-mortem* examination a tumour was found bulging into the Circle of Willis; it was whitish grey in colour, and about the size of a small tangerine orange, measuring 5 cm. by 4 cm. by 3 cm. It had a definite adherent, fibrous capsule, and was shelled out easily and completely. On section it showed numerous cystic spaces, some empty, others filled with gelatinous material. The tissue was in some parts cartilaginous, in others soft, and contained gritty particles.

Microscopical examination showed that the tumour was composed of epithelial tissue surrounding spaces filled, in some cases with homogenous material, in others with myxomatous tissue. At the edge of the space the epithelium was columnar and stained deeply; below this columnar layer the cells were oval or cuboid in shape, and stained badly. Some cells contained several nuclei, and these were poor in chromatin. In places the cellular tissue was invaded by mononuclear cells and some multinucleated cells were seen. The homogeneous material seen within the spaces in some cases took the basic, in others the acid dye. The spaces filled with myxomatous cells showed a hyaline matrix in some parts, and here the tissue was extremely vascular and small hæmorrhages had evidently occurred. There was some true formation of cartilage which in parts had been infiltrated with calcareous salts. In the myxomatous tissue of one part large cells resembling the nervous elements of the retina were seen.

Scattered about the section, but most noticeable in the interepithelial spaces, are cells with a dark round nucleus, about the size of that of a lymphocyte, but often having a considerable amount of protoplasm. The protoplasm differs from that of the lymphocyte in staining pink, and having, in the larger cells, a granular appearance due to eosinophil granules. The membranes over the growth and away from it showed some general thickening, and infiltration of the vessels with lymphocytes was seen in the former position. There were numerous concentric hyaline bodies scattered over the surface of the membrane in all parts.

*Case 7.—Adenoma of the Pituitary Body.*

H. R. H., aged 44. Had a history of a fall from a cart with injury to the head 12 months earlier, since when patient had complained of failing eyesight. He had been peculiar for six months, having frequent delirious attacks accompanied by nausea and retching. He was in Guy's Hospital before being admitted to the asylum, and their notes state that there was no papillitis (field of vision not mentioned). The reflexes were not exaggerated, lumbar puncture showed nothing abnormal, and there was no tenderness of the head.

On admission to the asylum he was confused and stupid, and often incoherent in his speech. He had coarse tremors, inco-ordination of upper and lower extremities, and unsteady gait. The knee jerks were brisk, but there was no ankle clonus.

A history of syphilis was obtained. After admission the muscular power remained good, but patient had a seizure followed by left-sided convulsions, loss of consciousness, collapse and death.

At the *post-mortem* examination the convolutions of the brain were found to be flattened, and a tumour about the size of a chestnut was seen in the region of the pituitary body. Both lobes of the pituitary were enlarged, the glandular portion more so than the nervous. The latter was pale in colour, but the glandular portion was a deep maroon colour, and of about the consistency of natural liver substance. The thyroid gland was natural, and there were some remains of the thymus gland present. Other pathological conditions were old perihepatitis and cystic kidney.

Examination of microscopical sections of the tumour showed a uniform growth of small cells with darkly staining round or oval nuclei and protoplasm, varying considerably in amount, but always staining a clear pink colour with the I. G. stain. The glandular portion of the tumour was extremely vascular, large and small vessels abounding in all parts, and there was evidence of diapedesis and small hæmorrhages in places. No lymphocytic infiltration was seen; the nervous portion of the pituitary body, although white in colour to the naked eye, yet showed microscopically a growth of similar cells to those of the vascular portion. The vessels were much fewer in number, and the cells less distinct from one another.

In well-stained specimens of the I. G. method, many small cells varying from  $1\mu$  upwards were seen, but most of them were very minute. The membranes over the tumour showed an infiltration with tumour cells, but no obvious small round cell infiltration. Over the vertex in the ascending frontal regions, the membrane showed a slight lymphocytic infiltration around some of the vessels and small groups (about six or eight) of tumour cells clumped together.

*Case 8.—Choroidal cell growth in 4th Ventricle.*

E. W., aged 31 years. Was transferred to the asylum from the union as a case of puerperal mania.

There was a history of the birth of a living child five weeks before admission, after three pregnancies resulting in miscarriage or still birth. The patient had complained of great thirst three weeks before admission, was always drinking, and was greatly emaciated. In the Infirmary she failed to recognise her friends, was excited, noisy and restless, and had hallucinations. Later she became depressed, but was always ravenously hungry and thirsty. On admission to the asylum there was air hunger, but no physical signs in the chest. The urine had a Sp. Gr. of 1042 and sugar was present in large quantities. The patient was dull and unable to give any account of herself. The pulse was rapid and feeble. Temperature 96. Patient vomited twice on November 6th, became comatose, and died on November 7th, two days after admission.

At the *post-mortem* examination the pancreas appeared normal. There was chronic thickening of the pleure and some dilation of the right side of the heart. On removing the calvarium there was a slight excess of cerebrospinal fluid and the surface of the brain appeared normal.

Bulging into the calamus scriptorius of the fourth ventricle was a small firm tumour about the size of a pea.

Microscopical sections of the growth showed a small area of choroidal epithelium, surrounded by a comparatively deep and well-marked margin of fibro-neuroglial tissue. It was the latter which had invaded the substance of the medulla and caused pressure on the nuclei in the region of the calamus. The vessels in the medulla were dilated and in some cases surrounded by lymphocytes.

Sections of the cortex taken from the motor region showed a slight but undoubted infiltration of small round cells in the neighbourhood of the vessels. The nerve cells showed disorganisation, chromatolysis, eccentricity of the nucleus, and an irregular disposition of the cells with regard to the cortical surface. Some phagocytosis was apparent, but the cortex was markedly infiltrated with adventitial cells.

The membranes showed a patchy increase of small round cells about the vessels, more marked in some parts than others, but not confined to the occipital region of the growth.

*Case 9.—Endothelioma of the right frontal lobe.*

J. C. A stonemason; was admitted to Charing Cross Hospital complaining of headaches for a year (continuous during the past two months), nausea, fits, and loss of power over the legs. Just before admission he began to have incontinence of urine and faeces.

He suffered from complete loss of memory, always complained of feeling cold, was always sleepy, and generally appeared to be crying. There was well-marked optic neuritis in both eyes. After admission his temperature rose to 103.2° F. He had two fits, and later lost the power in his trunk muscles, and had to be lifted in and out of bed.

At the *post-mortem* examination the right hemisphere was found to contain a tumour about the size of a pigeon's egg in the frontal lobe. It only appeared on the surface at one point. The substance of the tumour was firm and vascular, pinkish grey in colour with irregular streaks of yellowish matter suggesting a "regressive metamorphosis." There was an area of softening around the tumour. Both ventricles contained blood-stained fluid, and there was a hæmorrhagic area in the posterior part of the pons.

Microscopical examination of the growth showed cells of two types. 1. Large epithelial cell, columnar or cuboid in shape, at places arranged in alveoli, and divided by broad areas of fibrous tissue. 2. Smaller cells with a clearer protoplasm staining more pink than violet by the I.G. method, and having dark nuclei; these occurred in patches or elongated strands, and in some cases were seen as circular inclusions within the protoplasm of the larger cells. These small cells show a greater tendency than the large ones to a regressive metamorphosis. In some places the strands formed by them had completely degenerated and appeared almost structureless. In other places complete strands show healthy cells, but of quite a different character from the large epithelial type.

There was some overgrowth of fibrous tissue around the vessels, and a lymphocytic reaction around the vessels at the edge of the growth. The brain substance beyond the limits of the growth was infiltrated for some little distance with multinucleated cells. The membranes in this case showed a well-marked small cell infiltration around the vessels, but there was no general thickening of the membrane, and no obvious endothelial proliferation.

*Case 10.—Multiple secondary Carcinomatous growth of both hemispheres.*

A. L., aged 50 years, had the left breast removed for cancer about six months before admission to the Asylum. On admission there was recurrence in the scar and surrounding skin, and enlarged glands in the left axilla.

At the *post-mortem* examination the axillary and supraclavicular glands were found to be enlarged and hard, and some of the mesenteric glands were also affected, but no malignant disease was found in the mediastinal glands nor in any of the abdominal or thoracic organs. An enlarged mass of glands surrounded the carotid sheath on the left side. On removing the calvarium the dura was pale, but not adherent. The convolutions of the brain were largely obliterated, and the pia was adherent to the cortex in many places. Multiple areas of new growths were found in both hemispheres, involving all the lobes. The Sylvian fissure could not be opened without tearing the substance of the brain, on account of multiple growths along the course of branches of the middle meningeal vessels. On microscopical examination the growth was seen to consist of irregularly spheroidal cells arranged in columns or groups, often incompletely separated one from the other. Strands of fibrous tissue occurred varying very much in amount in different sections. The nuclei of the cancer cells stained faintly in the majority of cases, and the protoplasm was often vacuolated and contained inclusions in many parts. Numerous definite atypical pink cells with dark nuclei were seen free, both among the cancer cells and in the nerve substance beyond the edge of the growth. Many of the cancer cells contained myelin debris within their protoplasm. Sections of the glands showed a similar structure, but fewer inclusions were seen, and the cancer cells had a tendency to be more cubical and better formed than in the cortex.

Some of the vessels of the cortex in the neighbourhood of the growth were infiltrated with round cells (Plate I., Fig. 1), and others were surrounded by single or double layers of cancer cells which were obviously spreading along the perivascular lymphatics.

The membranes in the parts examined showed some slight thickening and a patchy infiltration with lymphocytes around the vessels over the area of the growth. These changes were less marked than in some of the gliomatous tumors.

*Case 11.—Multiple secondary Sarcomatous Growths in both hemispheres.*

H. J., aged 53, was stupid, but able to converse rationally until one month before death. She then became resistive, troublesome, and very restless. Jactatory movements of the arms appeared, with exaggerated tendon reflexes, and Babinski's sign was present on the right side. Death ensued from progressive asthenia.

At the *post-mortem* examination a mass of new growth was found at the root of the right lung extending into all three lobes. The bronchial glands were involved, and there were multiple areas of new growth in the brain. These areas were pinkish in colour, and in the centre contained clear gelatinous matter of a semi-fluid consistency.

Microscopic examination of sections of the tumour in the lung showed a cellular growth, the cells for the most part being small and round, or oval with very little intercellular fibrous tissue, but in some sections, both of lung and brain growths, there were definite clumps of larger cells of the endothelial type, and all degrees can be seen from these to the small round cells, although the latter predominate. The pink bodies with dark nuclei in sections stained by the I.G. method are well

seen as inclusions in some parts of the sections, and numerous tiny cells having a similar staining reaction are seen scattered among the small round cells of the growth.

The membranes were not greatly thickened, but there was a well-marked lymphocytic infiltration around some of the vessels.

*Case 12.—Endothelioma growing from the Dura Mater.*

E. T., aged 80 years, was depressed on admission, and had auditory hallucinations. The pupils were unequal, but reacted to light and accommodation. Death occurred from cardiac failure after a collapsed condition lasting several days.

At the *post-mortem* examination the lungs showed signs of broncho-pneumonia, and there was generalised arterio-sclerosis.

In the parietal region of the left hemisphere attached to the dura was a small circular circumscribed growth about the size of a small Spanish nut.

On microscopical examination the growth was seen to consist of elongated and spindle-shaped cells with round or oval deeply staining nuclei. There was some slight round cell infiltration at the base, and the growth contained vessels with well-formed walls. No inclusions or atypical pink cells were seen.

*Case 13.—Endothelioma growing from the Dura Mater.*

E. D., aged 63 years, had dysentery after admission, and died of acute bronchitis.

At the *post-mortem* examination evidence was found of broncho-pneumonia, obsolescent tubercle of the lung, senile arterio-sclerosis, atheroma of the valves, and hypertrophy of the left side of the heart.

In the temporal region of the left hemisphere of the brain, apparently enclosed between the layers of the dura mater, was a small tumour about 5 mm. in diameter, definitely circumscribed, soft in consistency, and whitish in colour.

On microscopic examination the growth was seen to consist of irregularly shaped cells and multinucleated protoplasmic masses. The nuclei were mostly pale and vacuolated. The growth was very vascular, the vessel walls ill-formed, and a considerable number of red corpuscles were lying free in the tumour. There was a diffuse lymphocytic infiltration and some strands of fibrous tissue. The tumour was growing from and spreading along the inner surface of the dura. No inclusions or free atypical pink cells were seen.

*Case 14.—Endothelioma growing from the Dura Mater.*

M. A. S., aged 74 years, was stated to have had fits, but number and time were not given. She died of bronchitis.

At the *post-mortem* examination a small nodular growth was found in the right parietal region near the longitudinal sinus. It was about the size of a Spanish nut, and soft and friable to the touch.

Microscopical sections of the growth showed elongated spindle-shaped cells with oval nuclei and irregular protoplasmic masses containing several nuclei. The growth was vascular with free red corpuscles scattered through the substance.

The tumour appeared to arise from the endothelium lining the dura mater; and was quite localised.

*Case 15.—Multiple gummata of brain and spinal cord.*

E. D., aged 44 years. Suffered from insanity with gross brain lesion. Her speech was typically paretic, she had right facial paralysis and spasticity of the right arm and leg with Babinski's sign on the same side. Her right pupil was the larger, and both were sluggish to light: she had grandiose delusions and feeble health generally. She was collapsed for three days before death, and had considerable difficulty in swallowing.

*Post-mortem Notes* (from Horton Asylum).—The pupils were equal. The dura mater thickened and adherent to the pia at the base. There was excess of cerebro-spinal fluid. The pia was irregularly thickened, and there were numerous spindle-shaped thickenings at the branches of the vessels. The ventricles were dilated and granular. Attached to the membranes on the roof of the 4th ventricle and spreading over the right superior peduncle of the cerebellum was a small tumour, larger than a pea, and not so large as a filbert. It was uniformly yellow in colour, of the consistency of firm fat, and appeared to be attached to the pia. There was some general atheroma of the vessels, evidence of an old perihepatitis, and the capsules of the kidney were thick and adherent. The tumour on the right superior cerebellar peduncle was yellow in colour, measured 1 cm. by 5 cm. in diameter, and extended down into the substance of the medulla. On the spinal cord were numerous small hard white nodules. At the level of the 7th cervical segment was a small growth involving the postero-lateral region on the right side; in the cervical and dorsal regions were various nodules on the posterior roots, and in the dorsal region a few nodules in the substance of the dura.

Microscopical sections of the tumour on the superior cerebellar peduncle showed a uniform growth of fat cells and fibrous tissue. The former was most abundant at the free edge of the tumour, while the fibrous tissue formed the base, and infiltrated the medulla beneath.

The nodules on the cord were uniformly cellular growths of a gummatous nature, and there was a very marked small round cell infiltration round the vessels in the neighbourhood, and also of the pia mater in all regions. No cell inclusions were seen in any of the sections and no cells taking the typical pink colour with the I.G. method, although the tissue was breaking down in some parts. Some scattered cells with dark crimson eosinophil granules were present in the gummatous areas.

The cortical cells of the motor region showed a curious vacuolation of their protoplasm. On staining with Scharlach's stain and Sudan III. these cells were seen to contain granules which took the characteristic deep red reaction given by fat.

The cortical vessels showed obliterative endarteritis and some periarteritis.

Sections through the medulla at the level of the 9th nucleus showed:—

1. Cell infiltration of the floor of the medulla with curious excrescences consisting of glial cells and fibrous tissue.
2. Cell infiltration around the vessels and in the pia with some new formation of fibrous tissue.
3. In the region of the 9th nucleus two small areas of hæmorrhage.
4. Chromatolysis and degeneration of many of the nerve cells of the nuclei.

The membranes of the brain showed a considerable degree of endothelial proliferation; it was not more marked around the vessels and no small round cell infiltration was seen in membrane removed either from the medulla and cerebellum or the vertex.

There was, however, a very noticeable lymphocytic reaction in some parts of the membrane of the spinal cord.

*Case 16.—Fatty tumour at the posterior border of the splenium, involving the fibres of Lancisi.*

A. B., aged 41 years, suffered from chronic dementia and died with symptoms of broncho-pneumonia after developing gangrene of both feet, accompanied by purpura of both legs.

At the *post-mortem* examination all the convolutions of the brain were found to be wasted except those of the occipital lobe. There was a small yellowish tumor lying between the hemispheres at the posterior end of the corpus callosum. The ventricles were dilated and granular. On examination, after hardening, the fibres of Lancisi lying on the upper surface of the corpus callosum appeared to become gradually thicker as they proceeded backwards. At the posterior border of the splenium they became continuous with a small yellowish nodule 1 cm. in diameter, which was attached to the callosal fibres, but did not appear to infiltrate below the surface.

Microscopical examination showed that this small tumour consisted of a uniform growth of fat cells with very little fibrous tissue; it was quite superficial, and did not infiltrate the corpus callosum.

The membranes were very little affected. There was some general chronic thickening and practically no infiltration of the vessels with small round cells.

*Case 17.—Gumma of left frontal hemisphere.*

E. F., aged 34 years. Had a typical history of syphilis with a premature climacteric six years before admission. There had been gonorrhœa two years, and pneumonia and pleurisy one month before admission. After the latter illness fits commenced and increased in number until before death she was having three or four every day.

At the *post-mortem* examination the dura mater was thick and adherent over the frontal region of the left hemisphere, and on section a gumma was found spreading into the hemisphere from the surface. There was also a gumma involving the whole of the superior and middle convolutions of the right hemisphere, and extending backwards as far as the ascending frontal convolution, but apparently not involving it. The gummata were indurated outside and caseous internally. On the right side there were no adhesions to the dura.

There were multiple hæmorrhages in the pons and medulla. The vessels in the Sylvian fissure on section showed crescentic, endothelial thickenings. Other pathological conditions found were evidence of old perihepatitis and some atheroma of the aorta.

On microscopic examination sections from the centre of the mass showed structureless material with debris of cells and nuclei. At the edges of the growth there was lymphocytic infiltration, and in some parts formation of true fibrous tissue. There was new formation of vessels at the limits of the growth, and dilatation of perivascular lymphatics without much endothelial proliferation.

Strands of fibrous tissue, carrying newly-formed vessels, ran into the substance of the brain tissue, and the capillaries in the neighbourhood were dilated. At the growing edge of the tumour, spreading into the brain substance, were large round

mononuclear cells of the variety usually seen in syphilitic lesions of the brain. They have a relatively small nucleus (about the size of that of an ordinary lymphocyte) but protoplasm, measuring often 30 to 40  $\mu$  in diameter.

The membranes in this case showed a very dense infiltration with lymphocytes over the growth and some proliferation of endothelium, the change being an acute one, as the membrane was not much thickened. In the portion of membrane taken from the occipital pole, there was a slight general overgrowth of endothelial cells, but no marked infiltration around the vessels.

*Case 18.—Caseating Tubercles of Cerebellum and left frontal.*

H. T., aged 6½ years, was admitted to the Great Ormond Street Hospital on July 7th, 1907, and died on August 25th. There was a history of frontal headache, and pins and needles in the limbs for the past four weeks, irregular vomiting for seven days, and diplopia for four days before admission. The child had had abscesses on face, chest, and thigh during the previous three months, which were thought to be tubercular.

On admission the temperature was normal, the pulse 100 and irregular. The mental state was normal, pupils equal, and active. There was no paresis of muscles, but König's sign was present. The knee jerks and plantar response sluggish. There was double optic neuritis. After admission the patient developed some right facial paralysis, and weakness of right arm and leg. The right cerebral hemisphere was exposed and the brain explored, but no tumour was found. After the operation, the child developed right-sided convulsions, and a fortnight later the left hemisphere was exposed, and a nodular growth felt anterior to the Fissure of Rolando, but no attempt was made to remove it. The child died one hour later.

At the *post-mortem* examination, generalised tuberculosis was found involving lungs, pleura, spleen, liver and kidneys, and the cervical bronchial and mesenteric glands. There was no ulceration of the intestines.

The brain was well convoluted, and showed a large area of bulging in the inferior parietal and superior temporal regions of the right hemisphere, and involving the region surrounding the posterior third of the Sylvian fissure. The bulging area was spongy to the touch, and the fissures of that part were shallower than those in other parts of the brain. On section a small pigmented spot was seen about 2.5 cm. below the posterior end of the Sylvian fissure, which suggested an area of hæmorrhagic encephalitis.

The left hemisphere showed a broadening of the upper part of the ascending frontal convolution, and on cutting through this area, two nodules of caseating tubercle were seen, one just above the genu, the other about 1 cm. from the mesial surface. In front a tubercular mass was seen to involve the whole of the white matter of the superior frontal convolution, but did not affect the cortex. The right cerebellar hemisphere was also the seat of a tubercular mass measuring 5 cm. by 2.5 cm. by 3 cm. The dentate and roof nuclei were not involved.

Microscopical sections of the growth showed caseating nodules with typical giant cells, epithelioid zone, and some patchy and diffuse lymphocytic infiltration which extended into the cortex around, but was not extreme in degree in any part. The endothelial lining of the capillaries showed slight proliferation, and the vessels in the membranes dipping into the fissures also showed this change, as well as some diffuse lymphocytic infiltration.



The medullary portion of the section of growth from the right hemisphere showed numerous small areas of encephalitis. These consisted of small patches of serous exudate surrounding vessels, with a smaller zone (immediately around the vessel) of cellular infiltration. The cells here, as has been noted by Oppenheim in similar acute cases, consist of mononuclear cells only, no polynuclear cells being seen.

The membranes over the tubercular area in the left hemisphere showed small, thick clusters of small round cells not always near vessels. There were an abnormal number of lymphocytes scattered over the membranes, but they had no especial relations to the vessels.

In the portion of membrane examined from an apparently unaffected part of the brain none of the above clusters of lymphocytes were seen, but there was some general increase in the number of lymphocytes present.

*Case 19.—Encephaloid Cancer of the upper lobe of the left lung.*

J. C., aged 71 years, suffered from bronchitis on admission to the Asylum, and died suddenly four days later.

At the *post-mortem* examination an ulcer was found in the duodenum about one inch from the pylorus. The ulcer was about 1 cm. in diameter, with clean-cut, slightly overhanging edges, and was somewhat œdematous, but not indurated. The floor was composed of muscle substance. The pancreas was not infiltrated, there were no adhesions, and no naked-eye evidence of malignancy.

In the centre of the upper lobe of the left lung was a whitish mass, which had every appearance of being a malignant growth—it was soft, whitish yellow, and had a well-defined edge.

Microscopical examination of sections of the duodenal ulcer showed no infiltration of the muscle wall with epithelial cells, and no obvious signs of malignancy.

The growth in the lung consisted of areas of epithelial cells, oval, cuboid, or columnar in shape, staining violet by the I.G. method. In the centre of these areas of epithelial cells were well-formed pink bodies of all sizes and shapes, often containing dark nuclei. Smaller bodies of this type also occurred as inclusions within the epithelial cells, and some were seen free in the lymphatic channels around the bronchi. They varied in size from 1  $\mu$  to 25  $\mu$  in diameter.

At the outer edge of the epithelial cell groups there was in some parts a well-marked small round cell infiltration. The lymphocytes in this infiltration differed very materially in size, shape and staining reaction from the pink staining bodies in the centre of the epithelial groups.

*Case 20.—Scirrhus Carcinoma of the pyloric end of the Stomach, and Fibroma over the left internal auditory meatus.*

R. T., aged 77, suffered from senile dementia and had presystolic and systolic cardiac murmurs. Three months after admission to Claybury Asylum she began to have œdema of the feet, and died suddenly 11 months later.

At the *post-mortem* examination the pyloric end of the stomach showed a diffuse thickening of the wall, which had the effect of narrowing the pyloric orifice. The mucous membrane was thickened and showed areas of patchy congestion. The pancreas was large, and had a swollen and inflamed appearance.

On removing the brain a small rounded tumour, soft and about the size of a Spanish nut, was found, lying over the orifice of the left internal auditory meatus.

It was not attached to the brain, but rested on the under surface of the cerebellum and although it lay beside the facial nerve was not connected with it.

Microscopical examination.—The sections from the pyloric end of the stomach showed a well-marked lymphocytic infiltration around the vessels, but no definite malignant growth was seen.

The section of the pancreas contained a small lymphatic gland which was attached to it, and lying between the fibrous tissue strands of the capsule were definite large epithelial cells, either singly or in groups of two or three. They had the characters of the cells of scirrhus carcinoma, and there was nothing to suggest that there had been sufficient inflammatory reaction to cut off pancreatic cells from the gland. In the lymphatic gland itself there were numerous elongated bodies staining almost black, which appeared to be some form of *saccharomyces*.

The liver showed some areas of badly staining tissue, and there was a marked small round cell infiltration around some of the larger vessels, with irregular strands of fibrous tissue running between the cells.

The section of the spleen appeared natural.

The growth at the base of the brain proved to be a cellular fibroma containing areas of vascular tissue surrounded by very poorly developed walls, the margin of the blood space being in some parts lined with fibrous cells only. There was some pigment in these sections.

*Case 21.—Cancer of the Stomach.*

F. G., aged 83 years, became emaciated, weak, and died of exhaustion after a fit. She had no symptoms of carcinoma of the stomach.

At the *post-mortem* examination a large fungating mass was found at the œsophageal end of the lesser curvature of the stomach. It extended through the stomach wall and caused adhesion to the left lobe of the liver behind, and there was considerable contraction of the wall of the stomach. There appeared to be no obstruction to the œsophageal opening, nor did the growth involve the œsophagus in any way, but nodules of growth were found in the pancreas, mesentery, mediastinal, and cervical glands.

Microscopical examination of the growth showed groups of cuboid and columnar cells separated by fibrous strands. The growth invaded the muscle tissue, and spread under the cardio-œsophageal junction, but did not involve the surface epithelium of the œsophagus.

Clear pink cells, often containing bi-partite nuclei, appeared in groups within the cancer cell areas, and were also seen in groups in the muscle tissue without being surrounded by cancer cells.

The secondary growths were of similar structure to the primary, with large areas of clear cells. The latter were numerous in the lymph channels, and in some parts of the kidney they were invading the substance without any cancer-cell intervention, sending up processes of growth and also scattered throughout the kidney substance, but the kidney cells did not appear to have become cancerous. They were degenerating, but not quickly dividing. The tissue showed very little sign of pressure from the growth. Some of the epithelial cells of the kidney were lying loose between the small infiltrating cells, and in some places the small cells appeared within the epithelial cells at the edges of the growth.

*Case 22.—Cancer of the Stomach.*

A. S., aged 69 years, died of progressive asthenia. A few days before death there was distention of the upper part of the abdomen and œdema of the feet. At no time was there either vomiting or constipation.

At the *post-mortem* examination an area of new growth, about 3.5 cm. in diameter, was found at the œsophageal end of the stomach, and there were several small polypoid growths near the pylorus. The whole of the liver was studded with secondary nodules, the lungs were infiltrated with new growth, and the omentum, kidneys, mesenteric, mediastinal, and cervical glands were also involved.

Microscopical sections of the stomach growth showed a papillomatous mass of columnar epithelium. The epithelial cells were often several layers in thickness, and also formed groups. The lymphatic channels were crowded with lymphocytes. Cells staining pink with the I.G. stain could be seen on the surface of the epithelium, and as inclusions within the epithelial cells. The cancer growth was infiltrating and breaking up the muscle substance. The growth in liver, lungs, and glands was of the same nature as the primary focus. There were many inclusions to be seen, and in the liver some hæmorrhage had taken place. There was some small round cell reaction and formation of fibrous tissue in parts. In films stained by I.G. after fixation in alcohol the pink cells can be seen, although they are somewhat broken up.

*Case 23.—Cancer of the Stomach.*

E. N., aged 53 years. No notes of this case were available.

The *post-mortem* notes were as follows:—On the posterior wall of the stomach was a circular ulceration about 2 cm. in diameter, having a raised, thickened, and infiltrated border. It was situated near the lesser curvature, about 2.5 cm. from the pylorus. The mucous membrane over the ulcerated area did not appear to the naked eye to be eroded except for a small area in the centre, but the surface was somewhat blackened. The liver was enormously enlarged, and most of the liver substance was replaced by secondary new growths, whitish yellow in colour, and firm except in the centre, where the growth was softer. The surface of the liver was irregular and nodular, and many of the nodules were umbilicated.

The gall bladder was shrunken and contained no bile, but 708 small faceted stones were found in it.

The pancreas was infiltrated with new growth, one nodule being the size of a walnut. The lungs contained many small nodules and bronchial, mediastinal, and mesenteric glands were involved.

Microscopical sections of the stomach showed irregular nodules of oval or cuboid cells among the muscle substance. There was very little small round cell infiltration. The growths in the liver, pancreas, and glands consisted of similar cells, with very little fibrous tissue. In the centre of these areas of cancer cells in some cases were cells staining pink with I.G. stain and having dark nuclei, and these cells were seen as inclusions in the growths in glands, etc.

In the lung tissue there was an early pneumonic change, with a good deal of fibrous exudation, some cellular proliferation and small-cell infiltration, and one or two foci of growth.

*Case 24.—Cancer of the Stomach.*

A. L., aged 64, began to have frequent attacks of vomiting one month before death, for which no physical cause could be discovered. This condition was progressive, and the patient lost weight, became very emaciated, and died of exhaustion.

At the *post-mortem* examination a malignant growth was found encircling the orifice of the œsophageal opening of the stomach. It spread for some distance along the greater curvature of the stomach, and was soft and œdematous at the edges. The stomach beyond the growth was small and contracted. There was no naked-eye evidence of involvement of any other organ or glands.

Microscopical sections showed that the growth originated in the epithelium of the stomach, the œsophageal epithelium being intact and apparently healthy, though the growth was infiltrating for a very short distance below the stratified cell area. The cells of the growth were cubical or oval in appearance, often vacuolated, and with nuclei poor in chromatin, and strands of similar cells infiltrated the muscle substance in all directions. The vessels in the underlying muscles were dilated, and there was a very marked small round cell reaction to the growth, small islands of tumour cells being surrounded by a dense wall of lymphocytes. Large areas of mononuclear and multinuclear cells were seen. The former often occurred within the protoplasm of the epithelial cells, the latter were free and formed large areas, confined within a limiting boundary of epithelial cells, and also lying free in the lumen of the superficial tubules. These cells had either clear or granular eosinophil protoplasm and dark nuclei.

*Case 25.—Carcinoma of Stomach.*

F. W., aged 65 years, died with no other symptoms than those of progressive asthenia.

The *post-mortem* examination revealed some degree of broncho-pneumonia and general arterio-sclerosis. On the lesser curvature of the stomach there was a small irregular lobulated growth, and beside this a second pedunculated one, each measuring about 2 cm. in diameter. The mucous membrane was intact over both growths. The stomach was not obviously thickened, but the whole of the stomach was congested, and this condition was most marked around the pylorus.

Sections through the growth when examined microscopically showed a papillomatous structure, consisting of an overgrowth of the glandular epithelium lining the stomach. The cells were for the most part only one layer in thickness, and were arranged on each side of fibrous tracts, carrying vascular or lymphatic channels. In one place the growth was infiltrating the muscle wall, and the strands of muscle tissue were broken up and to be seen lying between the cancer cell groups. There was a considerable amount of patchy lymphocytic infiltration, which in many cases was definitely surrounding dilated vascular channels.

The lumen of the epithelial tubules contained many atypical pink cells with dark nuclei, and similar cells could be seen in the lymph channels.

Another cell which appeared in large numbers in these sections was the swollen lobulated cell with definite divisions of the protoplasm, which are seen in many chronic inflammatory conditions.

*Case 26.—Carcinoma of Breast.*

E. L., aged 34 years, had the right breast removed for a hard mass felt in the lower and outer quadrant of the gland.

Microscopical sections made from the growth showed groups of epithelial cells, separated by thick bands of fibrous tissue, with a well-marked lymphocytic infiltration in some parts. The growth was that of a typical scirrhous glandular carcinoma mammæ.

The cancer cells contained as inclusions some small masses of protoplasm, staining a clear pink by the I.G. method, but very few of these masses contained nuclei.

*Case 27.—Carcinoma of the Breast.*

J. J., aged 80, collapsed suddenly while being forcibly fed during a period of maniacal excitement.

*Post-mortem* examination revealed a very hard nodule in the right breast, apparently a scirrhous carcinoma of very slow growth. The lungs and liver were studded throughout with nodules of new growth, and the bronchial and mediastinal glands were also affected. The thyroid gland was cystic and calcareous.

On microscopical examination the breast tumour was found to consist mainly of dense fibrous strands. At one end of a section a few islands of cells were seen scattered in the fibrous tissue. They were irregularly cuboid in shape, and occurred in small groups. Cells with pink protoplasm and dark nuclei were relatively numerous in this area. The liver showed areas of cancer tissue among the liver cells as paler staining patches, these areas not being cut off from the liver substance by fibrous tissue nor showing any evidence of round cell infiltration. The perivascular lymphatics of the portal system were infiltrated with the growth, and in some places masses of cancer cells were seen growing along the inside of the portal veins. There was some small round cell infiltration around the portal systems. Typical pink cells of all sizes occurred as inclusions and free among the cancer and liver cells. The cancer cells seemed not so much to be pressing on the liver tissue as replacing it, and in some cases the advancing edge of the malignant mass was formed of the clear cells with dark nuclei. The growths in the lungs showed similar cell formations, but the individual cells were larger. Several were joined together, forming multinucleated masses, and were apparently more quickly growing. Numerous inclusions were seen in these sections also.

*Case 28.—Carcinoma of the Breast.*

A. B., aged 65 years, was suffering on admission from recurrent carcinoma mammæ. There was a sloughing growth in the right breast which involved the skin, and the glands in both axillæ were affected. The emaciation was extreme, and death was due to exhaustion.

At the *post-mortem* examination nothing further was found except a small secondary nodule in the left kidney. There was no enlargement of mediastinal or mesenteric glands.

The growth in the right breast on microscopical examination consisted of groups and columns of cuboid or oval-shaped cells, divided by fibrous strands. There was little small cell infiltration around the growth, but under the skin in sections taken from that region the lymphocytic infiltration was quite massive. The epithelial cells of the skin contained as inclusions some of the bodies staining pink (with the I.G. stain), and containing dark nuclei, and these were seen also in and among the cancer cells. The growth was that of a typical scirrhous cancer of the breast.

*Case 29.—Cancer of the Breast.*

E. S. P., aged 68 years, had no available history beyond that of an attack of broncho-pneumonia.

At the *post-mortem* examination a hard nodule could be felt in the upper and outer quadrant of the right breast, which on section was extremely tough and fibrous.

On microscopical examination the growth showed dense fibrous tissue with islands of cells in small groups, and nodules separated by dense fibrous tissue. There was no small round cell infiltration. None of the pink cells with dark nuclei were seen in any of the sections, although many of the epithelial cells showed degenerative changes.

*Case 30.—Fibroma of left ovary.*

E. M., aged 33 years, suffered from puerperal mania. She had irregular pyrexia cough, etc., and died of pulmonary tuberculosis.

At the *Post-mortem* examination the left ovary was found to contain a yellow fibrous nodule, which on microscopic examination proved to be a fibroma.

The growth consisted chiefly of fibrous tissues, but there were many cellular areas around the vessels. The cells were chiefly connective tissue cells, but among them were cells with a relatively large amount of protoplasm for the size of the nucleus. This protoplasm was apparently breaking up into small greenish staining masses (I. G. stain), and the cells appeared to be ovarian epithelial cells. There was a well-marked infiltration with small round cells in some parts.

*Case 31.—Cancer of the Uterus.*

E.P., aged 62 years, about a month before death complained of pain in the back, and when examined by the medical officer was found to have an enlarged and tender uterus. The cervix was hard and puckered, and when the examining finger was withdrawn, it was covered with blood. A slight foul, blood-stained discharge was noticed afterwards, and the patient grew progressively weaker, but never became emaciated.

At the *post-mortem* examination the abdomen was distended, and about one to two pints of clear straw-coloured fluid were removed from the abdominal cavity. The whole of the great omentum and the serous surface of the large and small intestines were covered with small white nodules, and the mesenteric glands were invaded by a similar growth. The serous surface lining the abdominal cavity was roughened and congested. The liver was studded with several soft whitish nodules, and in one case a hæmorrhage within a nodule of growth.

The whole of the cervix and body of the uterus was replaced by malignant growth, making the organ completely unrecognisable, and fixing it to the rectum and bladder.

On microscopical examination sections of the uterine growth showed muscle tissue infiltrated with cells: some of the clusters were definitely composed of cervical epithelium, but a myxomatous condition prevailed over large areas. There was some lymphocytic infiltration and fibrous tissue formation within the areas of growth, and through the muscle substance, and some new growth of capillaries in the myxomatous area.

The cancer cells were oval, cubical, or spindle-shaped. Mitotic figures were seen in many cells. The small bodies with pink protoplasm and dark nuclei occurred as

inclusions and free among the cancer cells, and in some places formed multi-nucleated masses. The secondary deposits showed a similar character to the primary, with rather less lymphocytic reaction.

*Case 32.—Papilloma of the Bladder.*

J. C., aged 84 years, began to have retention of urine in December, 1907, and later the urine contained pus. This condition persisted for some weeks, was followed by incontinence, and the patient died on January 25th from broncho-pneumonia.

At the *post-mortem* examination the bladder was distended, the size of the cavity larger than normal, and the walls thickened. It contained about three ounces of pus. The prostate was enlarged and contained a nodule, whitish in colour, about the size of a walnut, which appeared to be neoplastic. There were no other signs of new growth, and no glands appeared to be involved.

Microscopically the growth consisted of a groundwork of fibrous strands carrying blood-vessels. On each side of these strands were layers of epithelial cells, varying in depth and number. In some parts they formed large masses of typical cancerous cells.

In the centre of many of the alveoli areas of cells were seen with dark nuclei and a clear protoplasm, which stains yellow with Van Gieson's stain and pink by the I. G. method. The cells were irregularly columnar in shape near the vascular strands, but more cuboid away from them; they were often vacuolated and contained many inclusions.

*Case 33.—Papilloma of the Bladder.*

S. G., aged 61, had a lipoma of the shoulder and papilloma of the back. He passed blood in the urine two days before death, but he had been treated for this condition before being admitted to the asylum.

At the *post-mortem* examination the bladder contained about  $\frac{1}{2}$  ounce of pure blood. Growing from the posterior wall were two large papillomatous masses which occupied almost the whole of the interior of the bladder. They were attached to the bladder wall by narrow peduncles, and there was no naked eye infiltration of the muscle substance of the bladder, and no secondary deposits in any other organ.

On microscopical examination the growth was seen to be extremely vascular, containing vessels of all sizes, singly and in groups, and with walls varying in thickness and often ill-developed; in many places the walls consisted of a single layer of fibrous tissue. The cells were uniformly spindle-shaped, and under the high power could be seen to stretch across the vessels in many places. In some of the vessels there are many spindle-cells lying free in the lumen among the red cells and scattered among them, both within and without the vessel are irregularly rounded bodies having pink protoplasm and a small dark nucleus.

The growth was not infiltrating the muscle wall of the bladder in any of the sections examined, but the mucous membrane was separated from the underlying tissue by a space containing mononucleated and multinucleated cells.

*Case 34.—Cancer of the Kidney.*

H. D., aged 63, was emaciated, feeble, and subject to seizures, but had no symptoms of kidney disease, and died from exhaustion.

At the *post-mortem* examination a large, whitish, irregularly-shaped mass was

found to involve the upper third of the left kidney. The left suprarenal body was normal.

On microscopical examination the growth was found to be very vascular and to be formed by epithelial cells interspersed with strands of fibrous tissue. Around many of the small as well as the large vessels there was a well-marked small round cell infiltration. The epithelial cells varied very much in size and shape, some being cuboid, some around the vessels almost columnar, and many were vacuolated. They tended to be aggregated into small groups with fibrous strands separating one group from another.

The type of growth was that described by Hektoen and Riesenhan as hypernephroma of the kidney. The adrenal body in this case was normal in size and also in naked eye and microscopical appearance.

*Case 35.—Papilloma of the Bladder.*

A. B., aged 46, a miller, began to have hæmaturia in April, 1906. On examination *per rectum* the prostate was found to be enlarged, hard and tender. The urine was acid and contained blood and pus. In June, 1906, he had lost weight, and had periodical attacks of retention of urine. He became gradually weaker and more emaciated, and died in October, 1906.

At the *post-mortem* examination the bladder was seen to be distended and filled with thick yellowish blood-stained fluid. The mucous membrane was covered with massive papillomatous excrescences, very soft, friable and villous-like; the growth covered the whole of the inner surface of the bladder except at the upper pole, where the mucous membrane was thickened and sacculated. There was marked thickening of the muscle walls of the bladder, but no obvious enlargement of glands in the neighbourhood.

On microscopical examination the growth showed cell areas varying in size and separated by bands of fibrous tissue; there was some lymphocytic infiltration around the fibrous tissue and at the edge of the growth. The tumour was very vascular, the vessel walls in many cases being ill-developed. Clustered around the vessels and fibrous strands running from them were elongated cells with numerous nuclei; these latter took the stain badly and often appeared quite pale and vacuolated; the protoplasm took a violet colouration with the Giemsa stain. Some of these "cancer" cells contained typical "cell inclusions" with protoplasm staining pink and nuclei dark blue or black with the I. G. method, and in the centre of the larger groups of cancer cells these pink staining cells occurred free in groups. Sometimes they contained two nuclei, but there was no tendency to the multiplication of nuclei without cell division seen in the cancer cells proper, and each cell wall was for the most part separate from its neighbour.

*Case 36.—Adenoma of the right Adrenal Body.*

G. W., aged 53, was under observation for about eight months. He had no symptoms beyond a progressive asthenia, but became bedridden and died of bronchopneumonia, accelerated by fracture of the ribs and sternum.

At the *post-mortem* examination the right adrenal gland was seen to be enlarged, and on section a rounded mass, 1 cm. in diameter, was found bulging the capsule on one side. The remainder of the gland appeared normal to the naked eye.

On microscopic examination the rounded mass showed "skeleton" cells, large and



pale, and round or oval in shape. They occurred in small groups or columns separated by blood vessels distended with blood and occasional areas of round cell infiltration. A fibrous strand in part surrounded by hæmorrhage apparently carried a larger vessel across one edge of the adenomatous nodule. The medullary substance of the adrenal appeared normal in structure.

A few atypical cells with round, dark nuclei and clear pink protoplasm were seen scattered about the sections stained by the I. G. method, but they were not greatly in evidence and only noticed under systematic examination with 500 magnification.

*Case 37.—Carcinoma of the Large Intestine.*

M. E. D., aged 66, had no symptoms of disease preceding death, but collapsed suddenly when walking in the airing court, and died in a few minutes.

At the *post-mortem* examination collapse of the left lung, hydrothorax, chronic interstitial nephritis and general enlargement of the thyroid gland were found. There was a large fungating growth (the size of a tangerine orange) at the lower end of the cæcum, not involving the ileocæcal valve. No enlarged glands were seen.

Microscopical sections of the growth showed columnar epithelial cells, often atypical in form and with pale staining nuclei. The growth was infiltrating the muscular coat, and there was a considerable amount of small round cell infiltration at the margin.

In sections stained by the I. G. method, cells with pink protoplasm and dark nuclei appeared in great numbers, both free and as inclusions within the epithelial cells. They varied very much in size and shape, often appearing as small protoplasmic masses with four or five nuclei. Cells having a similar staining reaction were seen free in the lymph channels. A very marked feature in this case was the presence of the pink cells on the surface of the epithelium and within the surface epithelium.

*Case 38.—Adenoma of the Thyroid Gland.*

C. H., aged 57 years, died of pulmonary tuberculosis.

At the *post-mortem* examination tuberculosis of the lungs and tubercular ulceration of large and small intestines were found. The upper part of both lateral lobes of the thyroid glands were enlarged; on the right side a section cut through the enlarged portion showed yellowish cystic areas with a partly calcified wall; on the left side the centre was soft and reddish in colour, the capsule yellow and firm. There were no adhesions to the surrounding structures.

On microscopic examination the growth showed groups of glandular cells of various sizes, separated by strands of fibrous tissue. There was a well-defined fibrous capsule and a good deal of small round cell infiltration. The centre of the tumour was breaking down, but at some parts of the edge of the growth the granular cells were quite atypical both in form and arrangement, and there was a good deal of hæmorrhage into the tissue. The cells formed groups of five or six deep or were arranged in columns, and were often vacuolated and incompletely divided from one another. In one place the growth appeared to be spreading through the capsule. Hanging drop specimens made from this growth showed large spindle-shaped cells very different from those seen in film preparations and cut sections of the growth.

*Case 39.—Cancer of the left Adrenal Body.*

M. C., aged 73, began to have sudden attacks of dyspnoea in September, 1906, developed oedema of the feet and died of heart failure a month later, although no cardiac lesion was evident during life. There was dulness at the base of both lungs.

At the *post-mortem* examination about 10 ounces of fluid were found in the right pleural cavity and the surface of the lung was studded with white nodules. On section the substance of all three lobes was infiltrated with small white areas often showing punctate hæmorrhages. The upper lobe on the left was solid with a mass of new growth moderately soft in consistency. The lower lobe showed scattered islets of a similar nature. On the upper surface of the left adrenal was a round whitish mass about the size of a Spanish nut, similar in character to the growths in the lung. The lymphatic glands around the abdominal aorta were enlarged, soft and white, and the bronchial and mediastinal glands were also affected. There was a small polypus of the uterus.

Microscopical sections of the suprarenal growth showed areas of quickly growing cells with large pale nuclei, and with a protoplasm staining violet. Among these cells were masses of protoplasm staining a deep pink colour, which were for the most part non-nucleated, but in some places contained round dark nuclei. The same pink cells also occurred as inclusions within the cubical, violet staining cells, and could be seen lying free among suprarenal cortical cells, which were not malignant in character, *i.e.*, did not show signs of active proliferation.

Sections taken from the growth in the lung showed a mass of the pink staining cells surrounded by a considerable small round cell infiltration, but between the pink cells and lymphocytes there was always a zone of cancer tissue cells, mostly irregularly oval or cuboid in shape. These cancer cells contain many of the pink staining masses, nucleated or non-nucleated, as inclusions. The glands showed isolated areas and strands of the pink nucleated protoplasmic masses, and at first it appeared that none of the true cancer tissue cells were present, but one or two isolated elongated violet staining cells were seen lying in a lymph space.

The sub-mucous polypus was a simple, typical example of the glandular type, with columnar epithelium lining the spaces and a large amount of mucous glandular tissue near the base of the growth.

This tumour was of interest from the fact that microscopical sections showed that the growth was spreading in the same way as has been noted in the case of gliomata. Glandular cells beyond the malignant area showed early proliferation changes, and this in a less degree as they were further removed from the growth. There was thus a gradual transition from normal suprarenal epithelium in one part of the gland to quickly growing unhealthy cells in the tumour area.

*Case 40.—Cancer of the Gall Bladder.*

J. W., aged 64 years, began to have a rise of temperature in the evening about five months before death, sometimes as high as 103° to 104° at night and falling to normal or sub-normal in the morning.

There was some pain in the right hypochondrium, and on palpation a hard mass could be felt in the region of the gall bladder. This mass increased in size until (before death) it reached the mid-line of the abdomen. There was some ascites, about 100 ounces of fluid being withdrawn.

At the *post-mortem* examination about two pints of clear sherry-coloured fluid were removed from the abdominal cavity. Around the liver there were numerous and dense adhesions, fixing the transverse colon firmly to the under surface of a growth apparently arising in the gall bladder. The anterior surface of the liver was very granular, and at the inferior border of the right lobe there was a round thickened cartilaginous plate. The gall bladder was enlarged and thickened, and on section was seen to be infiltrated with new growth which had the appearance of being in a state of disintegration; embedded in it were four or five faceted calculi. Immediately underneath the cartilaginous plate referred to there was found in the substance of the liver a large area of new growth, definitely circumscribed, soft greenish yellow, and at the centre containing creamy pus. The pancreas presented an unusual appearance, containing dark maroon coloured areas scattered throughout the entire substance, apparently due to hæmorrhage.

Microscopically the growth was of the typical encephaloid cancerous variety, consisting of masses of more or less oval cells, taking a purple stain with the I. G. method. In the centre of these masses cells containing pink and containing dark nuclei were grouped, and the same occurred as inclusions within the tumor cells.

There was a good deal of fibrous tissue reaction around this growth, and in the substance of the liver; the small round cell infiltration was most marked around the portal tracts. The bile ducts appeared to be increased in number and size; there was an undoubted proliferation of the epithelial cells, and in some parts several layers of cubical epithelium could be seen lining the ducts.

Under a high power the malignant masses were seen to consist of cells which mostly contained pale staining vacuolated nuclei. The protoplasm between adjacent cells was continuous, and it was impossible to distinguish cell boundaries in many cases. The isolated cells were most elongated, and suggest a columnar celled growth. There was a marked intercellular cirrhosis of the liver, and the pancreas also showed a fibrotic condition with some hæmorrhage.

#### THE CEREBRAL GROWTHS.

The Notes of Cases 1 to 18 are those of tumours situated within the cranial cavity. Of these, 12 were primary in the brain or membrane, and confined to that situation; two were secondary to growths arising in the lung and breast respectively; three were syphilitic tumours, and one was tubercular. The four latter cases were included for comparison.

The clinical aspect of the cases does not come into consideration in the notes, but the question of the possibility of the presence of a demonstrable physical basis for the mental symptoms in cases of cerebral tumour has not been lost sight of. It has been suggested by Devaux, Dupré, and others, that a co-existing diffuse meningitis and encephalitis, as indicated by definite histological changes, may explain the onset of mental symptoms in cerebral tumor. A small round cell infiltration around the vessels of the cortex and membranes was present in 16 of the cases described above, but included among these is the case which died

in Charing Cross Hospital, in which mental symptoms were neither early nor obtrusive. Bruns, in the new edition of his work on "Tumours of the Nervous System," states that he does not consider that the changes seen around tumors are really inflammatory, and there appears some ground for believing, as will be shown later, that the infiltration by lymphocytes is not a truly inflammatory condition, but more probably due to the toxic action of the products of degeneration traversing the perivascular lymphatics.

Many other writers have discussed the origin of the mental symptoms in cases of cerebral tumour, and the general consensus of opinion is in favour of the view that their onset is influenced by the size and position of the tumour. Schuster inclines to the belief that the type of mental disturbance is dependent in some degree on the location of the growth, and finds active mental disturbance coincident with tumours of the frontal, temporal and occipital lobes, while simple mental failure is associated more commonly with growths in the parietal and callosal regions. This was not borne out in the above cases, since, in the four cases of insanity in which tumour was situated in the frontal lobes, the symptoms were those of simple dementia or dementia with delusions.

It is therefore impossible at the present time to correlate the presence of mental symptoms either with the position of the growth, or with the histological changes, and another factor must be presupposed.

The histological features which have been especially studied in the foregoing cases of tumor cerebri are those connected with the method of spread of the growth, the influence on the cortical elements, and the cell reactions and changes.

In the gliomatous tumours the growth appears to extend in two ways. In some places cellular areas of glia tissue can be seen invading cortical and medullary substance, and these areas are often, though not invariably, connected with vessels. But in other parts, where, apparently, nerve cells and fibres are still present, there seems to be a diffuse proliferative influence acting on the glia cells, decreasing in degree as the section is farther removed from the more cellular growth. This is shown by the gradual change in the number of neuroglial cells and the presence of two or more nuclei in one cell. In other words, healthy normal-looking brain substance passes insensibly into that containing a slight excess of neuroglial nuclei; this in turn is succeeded by tissue obviously containing neuroglia in abnormal proportions and accompanied by degenerated nerve-elements, and if the section be followed towards the centre of the growth, areas of cellular glial tissue are seen, in which no nerve elements are present beyond patches of degenerated matter.

This condition of growth of the tumour for which the brain, as an

organ, offers great facilities of observation, would appear to entirely negative the theory that the growth originates from a single cell or group of cells as far as gliomata are concerned. The condition appears to be due rather to an influence gradually extending beyond the part obviously affected, and so acting upon healthy neuroglia, that proliferation of existing tissue is induced over a considerable area. We are thus led to the conclusion that a glioma is the result of a tissue change, due to some undefined cause which transforms healthy neuroglial tissue into quickly growing gliomatous cells, and is not traceable to a growth from a definite cell or group of cells, embryonic or otherwise.

In Case 10, where multiple cancerous nodules occurred in both hemispheres, secondary to a carcinoma of the breast, the extension to the brain was obviously along the perivascular lymphatics by way of the carotid artery. The line of spread was visible to the naked eye along the posterior Sylvian branch of the middle meningeal artery, and Plate I. (Fig. 3) shows the growth spreading along a small cortical vessel. After considerable investigation of these cases I am not able to support the theory of Mr. Sampson Handley, that a small round cell infiltration is present when rupture of the lymphatic channel occurs from distension by the growth. It is certain that, in the brain, rupture of the lymphatic vessel by the growth may occur without any lymphocytic infiltration appearing round it (Plate I., Fig. 3), and equally certain, as shown in Plate I. (Figs. 1 and 2) that marked lymphocytic infiltration can be seen around vessels in which the tissues and perivascular lymphatics are quite free from any sign of cancer cells. It would perhaps be hardly justifiable to deduce from the above cases, that the lymphocytosis is not a primary tissue reaction to the cancer cell growth, but either secondary or the result of a common factor not yet demonstrated, but as the lymphocytosis without visible growth and the converse are found frequently in tumours of other organs, the weight of evidence is against the theory of mechanical injury.

The presence of metastatic groups of tumour cells scattered about the membranes as far as the vertex of the brain in Case 7, where the tumour was a circumscribed, localised growth of the pituitary body, is of interest. Metastases of primary growths in the brain are uncommon, but Hyde and Curschman describe a case of secondary cancer where the membranes were milky to naked eye appearance, and on section showed innumerable minute secondary foci. The growth in Case 7 was looked upon as an adenoma of the glandular portion of the pituitary body, and the structure greatly resembled that of a normal pituitary gland. The growth was very vascular, but the groups of tumour cells seen scattered over the membranes were not in any way connected with the vessels, and the only way

in which dissemination can have occurred appears to be through the cerebrospinal fluid. It is not easy to understand how the cells were given off from the tumour in such a way as to give rise to this condition.

The influence of new growths on the cortical elements has been incidentally mentioned in the case of gliomata in the foregoing paragraph. These tumours are purely an overgrowth of the neuroglia, and the convolutional outline in the majority of cases is but little disturbed. The tumours are mostly slow growing, and it follows that the destruction of cells and fibres is also a slow, though progressive process. As mentioned above, the cellular portions of these growths show comparatively little infiltration and gross pressure on the nerve structures around, and it may be that the overgrowth of neuroglia and the degeneration of nerve cells are due to a common cause. Both Bruns and Cornil and Ranvier comment on this gradually extending affection of the nerve elements in gliomata, but consider that it is due to the slow infiltration of the brain substance by the growth. In the case of the endothelioma and sarcoma and secondary growths, the infiltrating nature of the tumours cannot be doubted, and isolated islands of degenerating nerve substance show that the malignant cells have caused degeneration more quickly than it can be removed. But although the nerve cells in the immediate neighbourhood of the growth show chromatolysis and all stages of degeneration, the evidences of gross pressure on the tissues immediately surrounding the malignant areas are very few, and the manner in which the tumour cells are infiltrating and breaking up the nervous substance at the edge of the proliferating mass is markedly different from the action which infiltrating epithelioid or plasma cells have on the tissues in syphilitic areas. Perhaps the most striking difference is that in malignant growths, although the centre of the tumour may show necrosis, and small areas of degenerating nerve substance, yet for the most part, and especially at the growing edge, the nervous material is broken up and disappears, and does not remain as a caseating mass infiltrated with cells.

The influence of the tumour on the vessels of the cortex and membranes has been noted in most of the cases, and a small round cell infiltration of the vessels near the growth is a constant feature. This lymphocytic reaction is in many cases completely absent around the growth, and noticeably so in the gliomatous tumours, but it occurs around the vessels of the cortex and membranes, and is most marked in the proximity of the tumour, and usually less so as sections or membranes are examined further away from the affected area. Endothelial proliferation of the vessels and perivascular lymphatics was well-marked in three cases, but wherever it was seen this change was a slight and recent one, never in

the least resembling the endothelial proliferation seen in syphilitic vessels.

The perivascular lymphocytic infiltration apparently results in an increase of fibrous tissue around the vessels, since within the tumours the fibrous condition is the rule, while the lymphocytes appear in large numbers only at the edge or beyond the growing border of the tumour. Dilatation and new growth of vessels are apparent in portions of gliomatous tumours, and hæmorrhage, diapedesis, thrombosis and organisation of the clot are not uncommonly seen.

In tubercular areas the cell reaction in a greater or less degree surrounds a central caseating mass. Scattered lymphocytes can be seen approaching the area from the surrounding vessels, and epithelioid cells accumulate around the tubercular focus. In no case of tubercle which has been examined has an infiltration of lymphocytes been seen heaped up around the vessels, nor has marked endothelial proliferation been evident.

In gummata of the brain, epithelioid or plasma cells surround the caseating area, and further out large mononuclear cells of a uniform size, with small nuclei in proportion to their protoplasm, may usually be seen infiltrating the substance of the brain. The vessels in these cases often show proliferation of the endothelium, and there is frequently a marked lymphocytic reaction around, resembling that shown in Plate I. (Figs. 1 and 2).

The similarity of the tissue changes, and among them the cell proliferation around the vessels of the brain, in sleeping sickness and general paralysis of the insane, has been noted by Dr. Mott, and the resemblance of the changes around the vessel shown in Plate I. (Fig. 2) to those described by him are very marked. Bosc has also drawn attention to the similarity of tissue changes in cancer and some of the protozoal infections, and the above-mentioned changes occur also round the vessels in malignant tumours of other organs.

In malignant growths of the brain, epithelioid or plasma cells are not a marked feature. Endothelial proliferation, though present, is of slight degree in the vessels, though more marked in the membranes, and a lymphocytic infiltration is the prevailing reaction. But a third type of cell is present in most of these cerebral growths, which is not represented in any of the tubercular or syphilitic growths of the central nervous system which I have examined. This is a cell to be described more fully later, which occurs free and included within the protoplasm of other cells in secondary growth in the cortex, and which has been demonstrated in films of gliomatous tissue by newer methods of fixation and staining, and also in one case of sections of the growth. It is a cell which varies

in size from  $1\mu$  to  $20\mu$  in diameter, and is characterised by a dark, compact nucleus and a protoplasm taking the eosin stain deeply after mordanting with the iodine solution. In the small cells the protoplasm appears clear and transparent, but in the larger ones a reticulum can be seen which gives the cell an appearance of having granules which take a stain slightly deeper pink than the groundwork. Cells of this type have long been demonstrated in "cancer" tissue, and were found in the secondary growths in the foregoing cases, and also in the cancer of the pineal gland, but in the tumour of the pituitary body they were represented only by extremely minute bodies shown in Plate IV. (Fig. 1), which were almost too small for any definite statements to be made about them. Beyond the fact that they are tiny, nucleated masses of protoplasm, little can be distinguished, but in some instances they were certainly contained within the protoplasm of the tumour cells. Those figured in the plate were from the region of a vessel.

Sections of gliomatous tumours have furnished material for the study of another cell change resulting in a condition known as "Colloid" bodies.

Bevan Lewis describes these as round or oval bodies varying in size from  $6\mu$  to  $40\mu$  in diameter, and occurring frequently in the brain in cases of insanity. He says that they are unaffected by aniline dyes, and considers that the bulk of evidence is in favour of the view that they are colloid in nature, and are derived from degenerating myelin fibres. In gliomata tiny homogeneous bodies can be seen within the glial cells, most frequently in the neighbourhood of the vessels or at the edge of the cortex adjoining the membranes, and these bodies have been observed of all sizes from  $2\mu$  to  $15\mu$  in diameter. Although in their earliest stage they appear as minute homogeneous bodies within the protoplasm of the neuroglial cells, taking a faint blue stain with the Iodine Giemsa method, and pink in the Hæmatoxylin and Van Gieson sections, yet in some cases they occupy the whole of the cell and appear to include the cell nucleus. When seen free in the cortex, the larger ones possess an irregularly lobulated centre which stains blue with hæmatoxylin, and also with the Giemsa's solution, while the homogeneous peripheral portion stains pink.

In Case 1, these bodies were so numerous at the edge of the cortex in the Island of Reil that various experimental methods of staining were possible. It was found that they gave the characteristic blue violet colour reaction of Chitin when sections were treated with iodine solution followed by zinc chloride, the rest of the tissue remaining yellow.

When treated according to the method recommended by Bethe for staining Chitin these bodies appear green, while the rest of the tissue takes a dark blue colour, but this method of staining is not very convinc-



ing. When cut in extremely thin sections ( $2\mu$ ) the outer pink staining portion of the larger bodies is in some cases split or cracked in such a way as to suggest that the envelope is of a brittle nature. The bodies are completely dissolved by prolonged exposure to strong acids and to acidified chloroform. They did not in any case give the colour reaction of amyloid material, and in the tumour cases they occur in far greater numbers at the edge of the cortex than in the medullary substance. If these are the same bodies as those described by Bevan Lewis, the theory that they are formed from degenerated myelin fibres is not borne out in the above cases, since their development can be traced within the neuroglial cells.

#### NEOPLASMS IN OTHER ORGANS OF THE BODY.

In the remaining 22 cases of new growths in other parts of the body than the brain, the symptoms again play a minor part in the notes of the cases. This is inevitable in the majority of instances, since 12 out of the 22 gave no signs of new growth during life. Cases 34 and 37, although complaining of no pain yet had delusions connected with the diseased part, which seems to indicate that some sensory impressions were received from the affected area, although the patient did not translate the impression in the normal way. The absence of symptoms in Cases 30 and 32 is of interest considering the extent of the stomach which was involved; the absence of vomiting shows that the reflex nervous paths must have been much less sensitive than normal.

In considering the pathological anatomy of the tumours in these organs, the changes which will be dwelt upon are those which are common to the majority of the growths, namely, those connected with the origin and spread of the neoplasms and the cell reactions and changes which take place in and around them.

#### ORIGIN AND METHOD OF SPREAD.

The systematic performance of *post-mortem* examinations on all asylum patients has given an opportunity for the examination of some early neoplasms. Case 25, a small papillomatous growth in the stomach, on microscopical examination showed all the changes which are found more extensively in the larger malignant masses. These are an abnormal plication of the mucous membrane resulting from a rapid proliferation of the epithelial cells, a separation of the mucous from the muscular layer by an infiltration of mononucleated and multi-nucleated cells, and a tendency on the part of the columns and folds of epithelial cells to extend down into the muscle substance.

In this early stage inclusions of the mononuclear cells within the epithelial cells are seen, but a large proportion of atypical pink cells lie free in the folds and submucous spaces. In the larger growths in this situation, illustrations of which are given, the pink cells with dark nuclei are a prominent feature. They are seen in groups on the surface of the epithelium, in groups and singly included within the protoplasm and nuclei of the epithelial cells, lying free in the lymphatic spaces beneath the epithelium and in the secondary growth of Case 21, illustrated in Plate III., these cells were seen invading the kidney substance in far greater numbers than the epithelium of the cancer tissue, small groups of the latter occurring only at rare intervals in the section. The early growths seen in the suprarenal gland showed a similar condition to that seen in the cells in gliomata, namely, a gradually extending tendency in the glandular epithelium to proliferation. In Case 39 this was accompanied by the presence of the pink cells mentioned above, some of them lying beyond the area of active proliferation, and among apparently healthy columns of cells.

Thus the origin of these tumours also from a single cell or group of cells seems unlikely, or if this occurs, the malignant tendency must pass from the original cell to those surrounding it, and the contagion spreading in this manner continue until the affected area is cut off from the healthy portion of the gland by lymphocytic reaction and the formation of fibrous tissue.

We are therefore led to the conclusion that in some of the tumours originating in glandular epithelium also the growth is not due to an unending proliferation of a definite small group of cells, but to a gradually extending tendency to multiply which spreads around a given focus, as has been found to be the case in gliomata.

In these early cases the lymphocytic reaction was largely confined to the region surrounding the vessels, although no signs could be found of the malignant cells spreading in that direction. On the other hand, the pink cells are to be found in the perivascular lymphatics beyond the region of the growth, and lying among the cells which show some proliferation tendency, but are not yet malignant in appearance.

The lymphatic channels surrounding the growths have been carefully examined, and in very few of the cases has the epithelial growth been seen extending along them.

The spread of epithelial cells as a continuous extension of the primary growth along the lymph channels, as described by Mr. Sampson Handley, was seen in the above cases only in cancer of the breast, and never around the primary growth in other organs.

## THE CELL REACTIONS AND CHANGES FOUND IN NEW GROWTHS.

The lymphocytic reaction to malignant growths is a well-known feature, and has formed the basis of many discussions. Mr. Sampson Handley considers that an infiltration of lymphocytes around the growth is due to mechanical irritation and, in the case of epithelial masses spreading along the lymphatic channels, does not take place until the growth causes distension and rupture of the vessel it is invading. It was shown in the section on cerebral growths that rupture in that situation may occur without any lymphocytic infiltration surrounding the mass, and that conversely lymphocytic infiltration is more often seen around vessels which are entirely free from any sign of cancer epithelial cells in their neighbourhood. Although this condition is not so striking in other organs, it can be demonstrated in them also, and the comparison, for instance, of a tubercular nodule with its walls of lymphocytes, and an adenomatous or cancerous nodule emphasises the difference in distribution of these cells. In all the cancerous tissues the vicinity of the vessels forms a greater attraction for the small round cells than the growth itself, thus forming a resemblance to syphilitic lesions rather than tubercular. This naturally suggests that some toxin or irritating body is present or passing along those channels, and close histological examination fails to show that this irritant is the cancer growth itself.

## THE ORIGIN AND DISTRIBUTION OF THE ATYPICAL CELLS CONTAINING A DARK NUCLEUS AND EOSINOPHIL PROTOPLASM.

These cells are termed atypical, since they do not conform to any known type of body cell. As seen in sections stained by hæmotoxylin and Van Giesen's solution, the protoplasm appears yellowish brown, and the nucleus, which is very well defined, a brownish blue. This is shown in Plate III., in which sections these cells appeared in great numbers invading the kidney substance. The tissue was taken from Case 21, the primary growth being a columnar epithelial cancer of the stomach. In sections which have been mordanted by treatment with an aqueous solution of iodine in potassium iodide, and stained by Giemsa's fluid as described in the introduction, these cells stand out from the surrounding epithelial tissue by reason of their much more deeply stained nuclei and their pure eosinophil protoplasm, which is clear in the smaller cells but granular in some of the larger ones. Their appearance in the tumour was that of a pink cell with a blue-black, well-defined nucleus, which in no way resembles the more or less violet protoplasm and paler blue nucleus of the tissue cells around.

As seen in films and sections, the small pink cells bear a great resemblance to nucleated red cells, but when red corpuscles and the former pink cells lie side by side, the blood corpuscles are seen to possess a much more distinct coppery tinge with this stain. The size of these atypical cells is very variable; many have been seen and drawn that are extremely minute, so much so that they cannot be distinguished with a magnification of less than 1,000 and their diameter is less than  $1\mu$ .

As inclusions within other cells, they vary from about  $2\mu$  to  $8\mu$  in diameter, and in some cases of cancer of the stomach much larger multi-nucleated masses have been noted as inclusions. When lying free among the cancer tissue cells they average about  $12\mu$  in diameter. Unlike quickly-growing cancer cells, they seldom form multi-nucleated masses, though these may be seen, but the protoplasm of each cell usually appears to be distinct from that of its neighbour, and is irregular in shape.

The above cells not infrequently appear as masses of protoplasm without any nucleus both within and without the epithelial cells, and on this account give rise to the necessity of considering the possibility that they are some degenerate form of the cancer tissue. This possibility is enhanced by the fact that degenerated material also takes an eosinophil stain, and the position of these cells in the cases examined has not borne out the statement made by Plimmer of what we believe to be similar cells, that they do not occur in degenerating parts of the tumour, but at the growing edge. It is true that in our cases they have been found invading tissue on their own account, as for instance in Cases 21 and 39, and beyond the margin of the tumour cells proper, but in Cases 10 and 19 they occur within the mass of epithelial tissue, their relative position as regards cancer cells and small cell infiltration being well shown in Plate IV. (Figs. 7 and 13) from Case 19.

When seen as non-nucleated bodies within the protoplasm of cancer epithelium, they might well pass for a colloid degeneration of the cell, although their other features do not bear out this supposition.

It is believed that the cells described here are identical with those noted in the first place by Thoma as cell inclusions, and investigated in this country by Plimmer, Ruffer, Walker and others. They are mentioned by many writers as occurring in malignant growths, and when present in large numbers (as in some of our cases) are described as "a second type of cell with clear protoplasm and a dark nucleus."

The staining of all the tumours with the modification of the Giemsa method has demonstrated the identity of staining reaction of these clear cells with those found in fewer numbers in other tumours, and with the smaller bodies occurring as inclusions within the protoplasm of other cells.

Plimmer found them in 88 per cent. of his cases, but they were found only in 25 out of 36 of the above cases, or 70 per cent. Although it is believed that these are the same bodies as those described by Plimmer, it is impossible to be certain of that fact, as he describes them as having a small amount of protoplasm and a capsule, whereas by all the above methods of fixation or staining, no capsule has been demonstrated either in the sections, in stained films, or in hanging drop preparations. In the latter these bodies appear to be composed of a more highly refractile substance than the protoplasm of the cell which contains them. They may be nucleated, but are often not so. When stained with "vital" methylene blue, the refractile bodies take up the stain more quickly and more intensely than the cancer cells proper, but Toison's fluid appears to leave them unstained.

No cell of this type and staining reaction has so far been demonstrated in blood films or in syphilitic or tubercular tissue stained in the same way, and it was never found in films of the cerebral growths until a rapid method of fixation was adopted. In films prepared by the wet method the pink cells, though recognisable to an eye accustomed to looking for them, could not be demonstrated in any great numbers, and mostly occurred as non-nucleated masses. It would therefore appear that these cells break up very quickly in films fixed in the ordinary way, and require very quick fixation for their proper definition.

At least three explanations are possible as to the origin of these cells:—

1. That they are some hitherto little-known tissue cell brought into prominence by the neoplasm.
2. That they are some modification of the tumour cells themselves due to regressive changes.
3. That they are extraneous bodies.

1. In support of this supposition it must be urged that it seems the most probable solution. The cells are most certainly found on the surface of the mucous membrane of the alimentary tract, but they may have been exuded from the surrounding tissues where they occur in great numbers. The wide distribution of the cell is in favour of this explanation, for they have been found in malignant tumours of all varieties and in all situations, and in the lymph channels in all organs of the body affected by malignant growths. Their variation in size is not without analogy in the microblasts and megaloblasts seen in the bone marrow in pernicious anæmia, but their presence in the body as a normal constituent has not yet been demonstrated. If this solution is the correct one, it is rather difficult to understand why they should take up a position in the centre of the tumour

cells, and why they should appear in such great numbers on the surface of the epithelium in tumours of the alimentary tract.

2. The possibility of these bodies being due to a regressive change in the tissue cells of the growth seemed very great as long as the small cell inclusions and isolated free cells were looked upon as the only representatives of the class. But the newer methods of staining have linked these on to the larger cells, which have so wide a distribution that the theory of endogenous cell proliferation discussed by Virchow, Boyce and others is hardly tenable. The same may be said of the suggestion that these bodies were due to colloid degeneration of the tumour cells, since it seems hardly feasible that large areas of cells should show complete colloid degeneration of their protoplasm, and that no transitional forms should be seen between these cells and the tumour cells from which they might be formed. The bulk of evidence appears to be in favour of these bodies being distinct entities; their nuclei always differ entirely from those of the tumour cells, and it seems improbable that a nucleus such as is seen in the latter, with its chromatin broken up and arranged for the most part in a network, should have given rise to the dark mass seen in the cell inclusion without any intermediate stages being visible. The protoplasm of the inclusions also has very distinct characters; in the young and small cells it appears clear and homogeneous, but in the older and breaking down cells a distinct granular appearance is noticeable and depicted in Plate IV. (Figs. 12 and 13).

The presence of these pink bodies in films where they appear as extremely virile cells, having no degenerative character, and their occurrence in such varied structures as endotheliomata, gliomata and epithelial cancerous tissue is against them being a degenerative change, especially as we have shown that the degenerative changes, probably colloid in nature, which do take place in gliomatous tissue and which we have never found in malignant growths of other organs, show quite other characters than the atypical cell. As shown in Case 29, degenerating cells are also seen in the epithelial growth without any evidence of the pink cells either free or as inclusions, and this was in a case in which it may be presumed that the tissue reaction was sufficiently good to control and kill the growth. In a paper on cell changes in dourine and sleeping sickness the possibility of the inclusions seen in those tissues being due to degenerative change was considered. In those tissues a very prevalent form was a cell with a crescentic nucleus. It seems worthy of note that this crescentic form has not been seen in any of the tissues examined here either in the degenerating material or free in the tissues of either cancer, syphilis or tubercle.

3. No proof can be offered at the present time that the atypical cells

are extraneous in origin, although this view is held by many able pathologists. It is suggestive that they occur in such large numbers in both early and advanced malignant disease of the alimentary tract, and that they are to be seen in considerable numbers on the surface of the epithelium. It would appear also that they are capable of invading tissues in secondary growths without the intervention of the cancer epithelial cell, and that in the majority of growths examined their situation is in the centre of the epithelium, where tissue cells reacting to the growth would hardly appear. Their variation in size, the difference in character of their nuclei, and their reaction to the same method of staining as the bodies seen as inclusions and free in the tissue in dourine and sleeping sickness, are interesting facts, but in the absence of experimental inoculation into animals nothing definite can be said on this point.

#### TUMOUR CELL CHANGES.

Plimmer has pointed out that the cells in a malignant growth are not necessarily like their parent cells either in size, shape or staining reaction. The change in the type of cell has been very noticeable in some of the above cases. In Case 11 the growth consisted for the most part of small round cells, but a few areas consisted of larger oval cells of the type seen in the endotheliomata, and their position was such as to suggest that the larger cells formed the primary focus. In Case 31, again, cells were seen obviously stamping the growth as one arising from the epithelium of the cervix uteri, and yet the greater part of the primary malignant mass and the whole of the secondary consisted of elongated spindle-shaped cells. It has also been frequently noted how much the secondary growths in glands resemble one another; a columnar-celled carcinoma of the stomach or intestine frequently results in a spheroidal or cuboid secondary mass in the glands, which is hardly distinguishable from a secondary growth following cancer in the breast or other region.

The source of the extra nutritive material which is required for rapid formation of new cells has long been an object of inquiry. It has been mentioned above that in the larger secondary growths which infiltrate organs like the liver, signs of pressure on the surrounding tissue are rarely great, and in many places quite absent. In spite of this fact very little *débris* of liver cells is seen among the cancer cells, except at the growing edge, and in that situation the cancer cells can be seen in some cases enclosing, in others growing into and splitting up the tissue cells of the part. It seems not improbable that the cancer tissue may in this way acquire some of the nuclein and other material necessary for its growth. But, if we concede this, we have to consider how these cells,

which originally arose from the epithelium lining the stomach, acquired the power of breaking up and devouring other tissue cells, and for an explanation we must look to the early stage of a growth.

We saw there that the epithelial cells contained what we have called "atypical cells" within their protoplasm, and that these cells were often non-nucleated. Is it not possible that these cells, whatever their origin, may be responsible for the malignant character of the epithelial growth? It is obvious that the "atypical cells" consist of a nucleus and protoplasm. If these cells are ingested by the epithelial cells, and their nuclei absorbed, the cell having this extra supply of nuclein manufactured for it would start to proliferate, and it is not difficult to imagine that having once acquired the habit of ingesting animal cells, it would attack any other cells which it met, and that malignant cells do largely ingest such cells as leucocytes and lymphocytes is generally conceded. In this way it may ingest the connective tissue, eat its way through the muscle substance, and, increasing in strength and virulence as it proceeds, become truly cannibalistic and form the rapidly growing masses which are so often seen in secondary growths.

#### SUMMARY AND CONCLUSION.

It has been seen in the foregoing pages that in the case of gliomata of the brain and of primary tumours in some of the glandular organs of the body, the growth of the tumour is due, in part at any rate, to some influence which acts over a wide area and appears to extend gradually around a given focus, causing proliferation of the cells of the organ. In the cases examined this focus has been a definite area of malignant cells, and the proliferation has decreased the farther the section is examined away from the malignant area. The active influence which causes this gradually extending tendency to multiply is at present undetermined. The fact that the most marked lymphocytic reaction is found around the vessels in the neighbourhood of the growth suggests that some toxic or irritant body is present in, or passing along, the perivascular channels.

The source of the extra nutritive material required for the rapid proliferation of tumour cells cannot be definitely determined, but the conditions of growth in some of the larger organs, such as the liver and brain, suggest that the invading tumour cells are not only phagocytic and remove the dead tissue which they replace, but that they are definitely cannibalistic, and attack the living cells of the organs.

In 25 out of 36 cases of tumour examined by new methods of staining, cells are found which have a distinct coloration. They consist of an eosinophil protoplasm, which is clear in the smaller and younger cells



and granular in the older ones, and a well-defined dark nucleus, which is sometimes multipartite but more usually single. These cells occur free in the substance of the tumours, on the surface of the epithelial lining of the alimentary canal, as inclusions within cancer cells, free in the lymphatic spaces, and alone in large numbers in the tissues in cases of malignant growth. By these methods of staining the bodies differ from those described by Plimmer in that they possess no capsule, and their nuclei are not refractory to hæmotoxylin, although by the hæmotoxylin methods of staining they are not differentiated from the tissue cells around. It is believed that they have not hitherto been noted in gliomata, and their presence in considerable numbers around the vessels in the cerebral tumours and absence in syphilitic and tubercular lesions of the brain is significant.

In conclusion I wish to express my great indebtedness to Dr. Mott, the Director of the Laboratory, who placed the material at my disposal and has given every facility and much personal help in the examination of the above growths. The very excellent illustrations are the work of Miss Kelley, and were drawn for the most part by the aid of the Camera Lucida.

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#### DESCRIPTION OF PLATE I.

- FIG. 1.—A vessel from the cerebral cortex in Case 10, beyond the edge of the cancer growth showing infiltration with small round cells and no cancer cells. Stained by Iod., Giemsa method. Magnification 230.
- FIG. 2.—Shows a similar infiltration around a cortical vessel beyond the growth in Case 4 of glioma of the temporal lobe. Stained by Iod., Giemsa method. Magnification 280.
- FIG. 3.—A vessel in the vicinity of the growth from the same section as Fig. 1, showing extension of the cancer cells around a central vessel. Although the growth has obviously burst through the perivascular lymphatic channel at the lower margin, there is an entire absence of lymphocytic infiltration around the growth. Stained by Iod., Giemsa method. Magnification 520.
-

PLATE I.

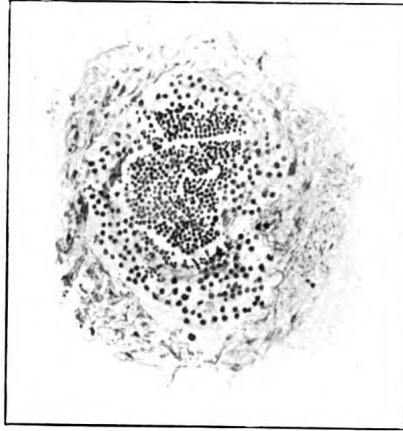


FIG. 1.



FIG. 2.

*Face p. 286.*



FIG. 3.



PLATE II.

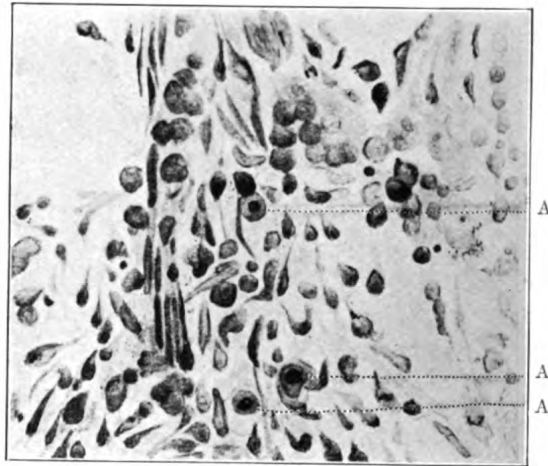


FIG. 1.

Film preparation from a glioma.  
A A A Atypical cells with dark nuclei. Magnification 400.



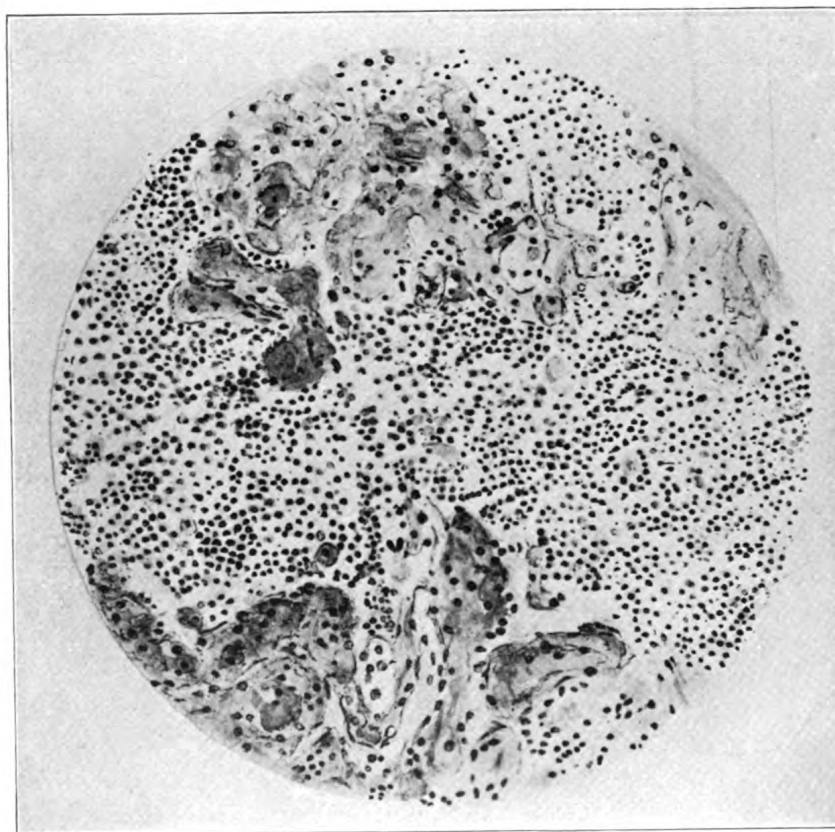
FIG. 2.

Cells from Fig. 1 under a higher magnification, with a typical  
glioma cell—B. Magnification 890.





PLATE III



*Face p. 287*



DESCRIPTION OF PLATE III.

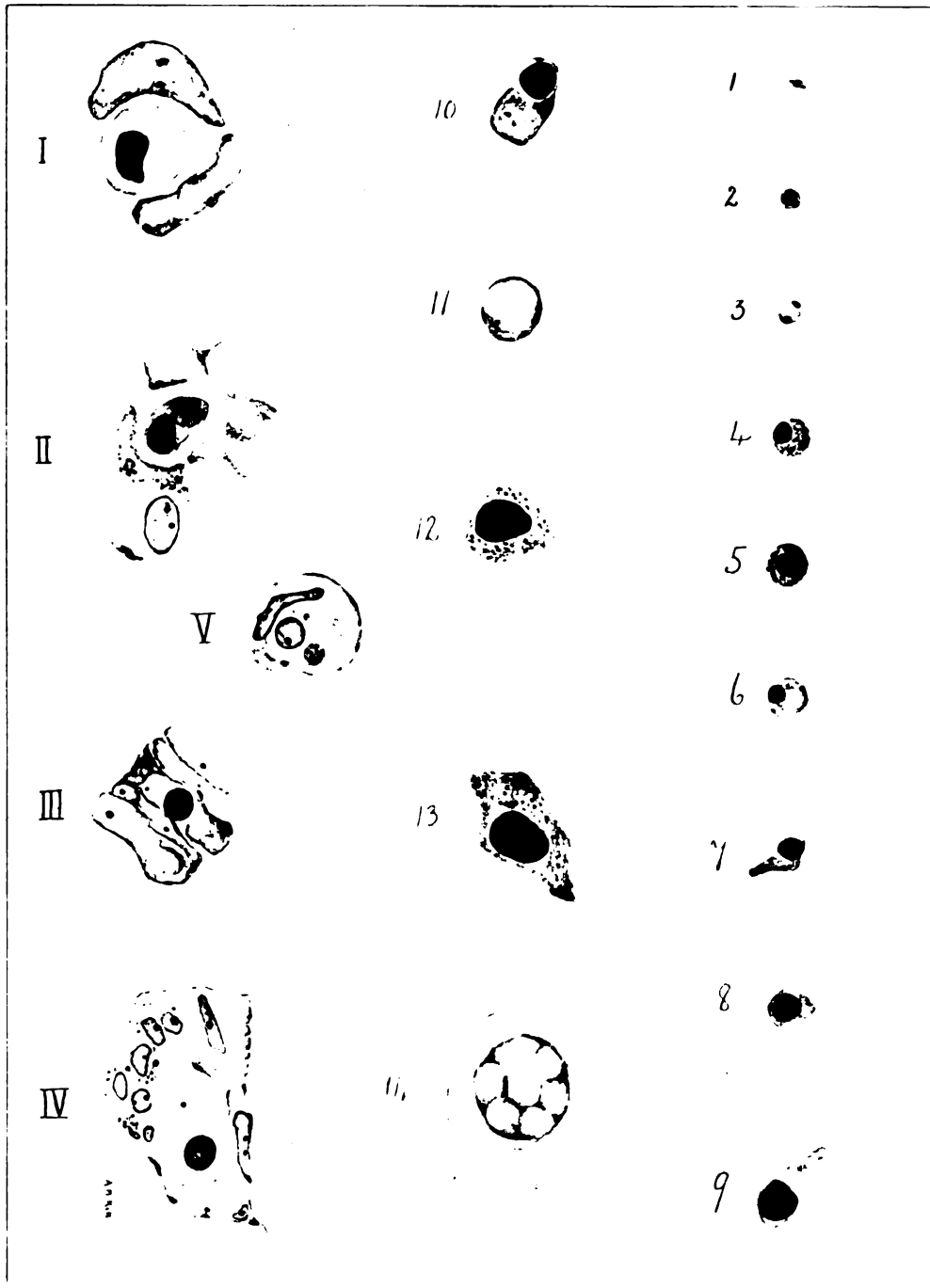
A secondary nodule in the kidney from a case of carcinoma of the stomach (Case 21), showing the mononuclear cells seen in the primary growth, but no columnar epithelium. Magnification 250.

## DESCRIPTION OF PLATE IV.

The atypical pink cells mentioned in the text as they appear free, and as inclusions in tumours.  
Stained by Iod., Giemsa method. Magnification 1,000.

- I.—A large cell (atypical) in cancer of stomach (Case 20, II.)
- II.—A similar cell, more deeply stained.
- III.—A small cell inclusion from a case of cancer of the intestine (Case 37).
- IV.—A similar cell from a case of Jensen's tumour in mice.
- V.—A cell with two inclusions, from the gland of a dog inoculated with *Trypanosoma Equiperdum*.
- 1 to 10.—Isolated cells of all sizes from different tumour cases. 1.—From Case 3.
- 2, 3, 4, 5.—From the lymphatic spaces of Case 19. The granular protoplasm in 4 and 5 is well marked.
- 6, 7, 8, 9.—From cases of Jensen's tumour in mice.
- 10.—From a hyaline space in tumour of the pineal gland.
- 12 and 13.—From a film preparation in cancer of stomach (Case 22).
- 11.—Is a red blood corpuscle, and 14 a cancer cell from the same film as 12 and 13, to show relative size.

PLATE IV.





## A DESCRIPTION OF THE BRAIN OF AN EPILEPTIC IMBECILE SHOWING EXTENSIVE HETEROTOPIA OF THE GREY MATTER.

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- I. History of the Patient.  
*Post-mortem appearance* of the external configuration of the Brain with weights and photographs.
- II. Description of internal structure with sections illustrating:—
  - I. Frontal region } vertical sections.
  - II. Central region } horizontal sections.
  - III. Occipital region.
- III. Account of the microscopical examination with illustration of cortex of the central region as compared with the same region in a normal adult brain and that of an infant aged six weeks.
- IV. Short account of cases hitherto described.
- V. Conclusions.

Through the kindness of Dr. Mott I have had the opportunity of examining the brain of a female epileptic imbecile who died in Claybury Asylum at the age of 37 years, which presents some interesting features.

*The clinical history* is as follows: As an infant she was very backward, could not walk until she was three years of age, and could only accomplish the most elementary acts. She was taught to dress herself, but never learned to sew or do housework, and could not be trusted to "run errands." She had no infantile illnesses, but when eight years old started to have fits at night and afterwards in the daytime. From that date she gradually became unmanageable, was sent to the workhouse at the age of 11, and from there to the asylum, where she has remained ever since. She was transferred to Claybury from Leavesden in July, 1906, on account of attempted suicide after a fit. She was said to be of quite the lowest type of humanity, of stout build (in a struggle which often occurred at bed-time she required five or six nurses to put her to bed), with a heavy under jaw and a powerful animal set of teeth. Her mental

state was that of complete imbecility; she could not recognise the doctor or nurse, and only knew three things—her dinner, which she gorged, an old rag doll, and some reels with which she was accustomed to play; with these exceptions she was oblivious to her surroundings. She was generally noisy and screaming, but her speech was childish; she would say, "Me want my reels." Her fits were typical and severe, occurring about twice a month and often at night; there was no *petit mal*.

She died of pulmonary tuberculosis with terminal gangrene. The parents were healthy; they had ten children of whom the patient was the eighth. The sixth child was also mentally affected at an early age and died in an asylum.

*Post-mortem examination.*—When the calvarium was first removed very little abnormal was noticed. There was slight thickening of the pia and a slight excess of cerebrospinal fluid. The brain weighed 1,040 gms., the right hemisphere 440 gms., the left hemisphere 415 gms., pons and cerebellum 155 gms., and the loss of weight after stripping the membrane was 35 gms. for each hemisphere. The normal average brain is about eight times the weight of its pons, medulla and cerebellum; consequently the deficiency of 200 gms. ( $8 \times 155 = 1240$ ) was an indication of failure of development of the cerebral hemispheres.

The brain was also under the average normal weight for that stature (Quain giving the average for 5 ft. 3 ins., the height of patient, as 1,218 gms.), and the loss from wasting, as estimated from the excess of cerebrospinal fluid and thickening of membrane, does not account for the difference; it was, however, not sufficiently undersized to be considered microcephalic. On examining the brain after removal it was found to be of a very low type of development. The most striking features were the shallowness of the sulci and an absence of frontal operculum which left the upper part of the insula uncovered; it was impossible to determine the upper limit of the Island of Reil from the external surface, but the small fissures (AA in photograph) probably represent the sulcus limitans insulæ. The *Sylvian fissure* slanted obliquely upwards on both sides, as is well shown in this photograph of the external surface (Plate I.), making an angle of  $47^\circ$  with a straight line drawn from the anterior to the posterior pole. The third frontal convolution was continuous with the Island of Reil along the whole length of the fissure on the right side, although in the left hemisphere there was a slight degree of overlapping in the parietal region. The remaining fissures were elementary; the fissure of Rolando was short and shallow, measuring (after hardening) only 5 mm. at its deepest point; the calcarine fissure ended at the posterior pole on both sides and the line of Gennari just beyond its termination. This latter fissure was the deepest in the brain (1.5 c.m.), the only other which

PLATE I.



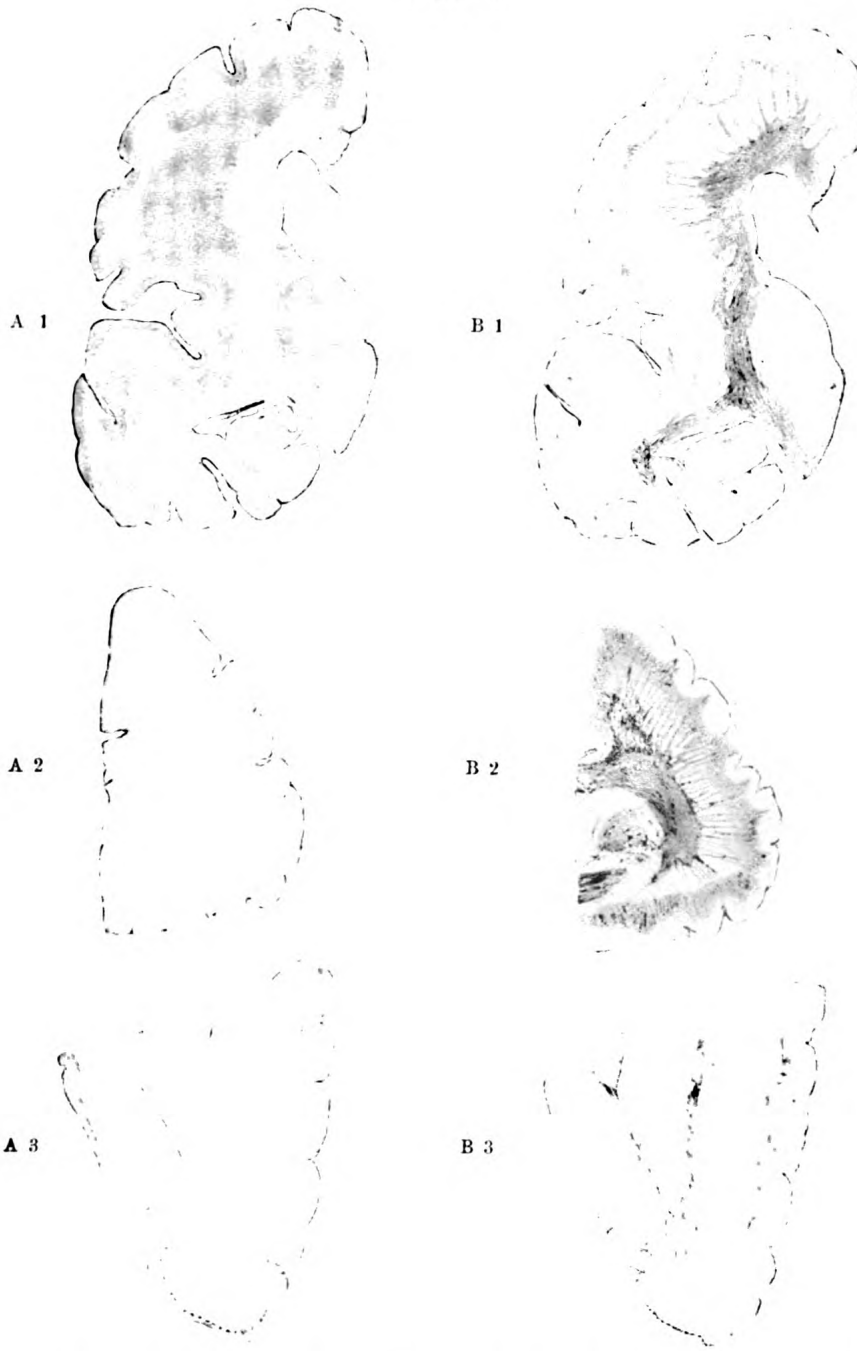
Photograph of right and left hemispheres of brain of epileptic imbecile, showing shallow fissures and poverty of secondary markings. A. A. slight indentations representing Sulcus limitans insulæ.







PLATE II.



- A 1.—A vertical section through the central region of the left hemisphere stained by Nissl's method for cells.  
 B 1.—Section from the same region stained by the Kulschitski-Pal method for fibres.  
 A 2.—Vertical section through the frontal region (Nissl's method).  
 B 2.—The same as A 2 stained by the Kulschitski-Pal method.  
 A 3.—Horizontal section through the occipital region (Nissl's method).  
 B 3.—The same as A 3 stained by the Kulschitski-Pal method.

approached a normal depth being the collateral, which measured 8 mm. at its deepest part.

The parieto-occipital fissure on both sides was shallow, especially at the mesial border, where the floor of the fissure was visible 3 mm. below the surface. The calloso-marginal fissure was fragmentary on both sides and ran within a few millimetres of the callosal fissure until it reached the central region.

The secondary fissures were short and shallow, the average depth of all sulci, with the exception of the calcarine and collateral, being 4 mm. The temporal lobe was best developed both in size and in the complexity of its convolutions.

## II.

*Internal structure.*—On section the cortex was found to be only slightly narrower than normal, but beneath the cortical grey matter throughout the whole cerebrum, with the exception of the fornicate and hippocampal gyri, was a deep grey band. On microscopical examination this band proved to be a second deep layer of nerve cells, which was separated from the cortex by a well-defined streak of white matter. The accompanying illustrations (Plate II.) were drawn from sections through the frontal, central and occipital regions.

Figs. A1, A2, A3, were stained by Nissl's method for nerve cells; Figs. B1, B2, B3, by the Kulschitski-Pal method for fibres. The approximate depths of the various regions are given below:—

DEPTH OF CORTEX.					DEPTH OF SUB-CORTICAL LAYER.		
Prefrontal	...	...	...	1.5 mm.	...	...	5 mm.
Frontal	...	...	...	1.5 mm.	...	...	9 mm.
Parietal	...	...	...	1.9 mm.	...	...	11 mm.
Occipital	...	...	...	1.5 mm.	...	...	8 mm.
Temporal	...	...	...	2.0 mm.	...	.	5 mm.

Accurate measurements were rendered difficult on account of the necessity of making an arbitrary point for the ending of the polymorphic layer, since in most parts the cells of that layer were continued down into the sub-cortical portion.

The cortical depth is rather over than under estimated, and, therefore, allowing for equal error in each case the occipital and temporal cortex show a preponderance over the other areas. The depth of the temporal cortex corresponds with the animal type of bodily development, and is an interesting feature. The sub-cortical layer tapered out just beyond the base of the calloso-marginal and collateral fissures, but microscopic investigation showed the presence of isolated cells scattered throughout

the white matter of these gyri. The sub-cortical layer appeared continuous with the claustrum, but a true claustral formation was wanting on both sides, the cells in this situation consisting of groups of pyramidal and other cells lying between the layers of fibres through which spindle cells were scattered. On the right side this region was broken up by a narrow, poorly developed band of white fibres, but no marked differences occur between the type of cell on either side of this division. The basal nuclei appeared normal in structure although the lenticular nuclei were smaller than usual, and consisted chiefly of putamen, the globus pallidus being only faintly indicated in naked eye specimens (Plate II., Fig. A1).

### III.

*Microscopical examination.*—The most striking histological feature in all regions of the superficial cortex was the immature condition of the cells and the deficiency in depth of the pyramidal layer. Fig. 2, Plate III., was drawn from a section taken from the top of the ascending frontal convolution, and to compare with it Fig. 1, Plate III., and Fig. 1, Plate IV., were taken from the same part of a normal adult brain and that of a six weeks' old infant respectively.

The abnormalities seen in this area are on the whole representative of those seen throughout the brain with the exception of the hippocampal gyrus, which approximates to the normal.

The cells in all regions are seen to be either embryonic or infantile; the outline is more often convex than concave and they have large nuclei and few processes. The zonal layer is narrow and either contains larger cells than are normal in this situation or the cells seen here really belong to the layer below; they do not conform to the three types described by Cajal, but are either round and quite embryonic or polygonal.

The small pyramidal cells are crowded together, are more triangular in shape than is usual, and the nuclei are large and pale.

The average size of the medium pyramidal cells is smaller (16 by 8) than in the normal cortex; the largest cells noted in this layer measured 24 by 11. Both this layer and the last are narrower than normal, as is seen from a comparison of the strips (Figs. 1 and 2, Plate III., and Fig. 1, Plate IV.), which were drawn with the same magnification by means of the camera lucida.

The large pyramidal layer in the central region contains cells up to the size of 32 by 19, *i.e.*, practically the normal size, but very few had any indication of Nissl granules. The Betz cells were somewhat abnormal in distribution. On the lateral surface of the hemisphere they were only found in about the upper fifth of the ascending frontal

PLATE III



FIG. 1. Strip of normal cortex, central region (Nissl).

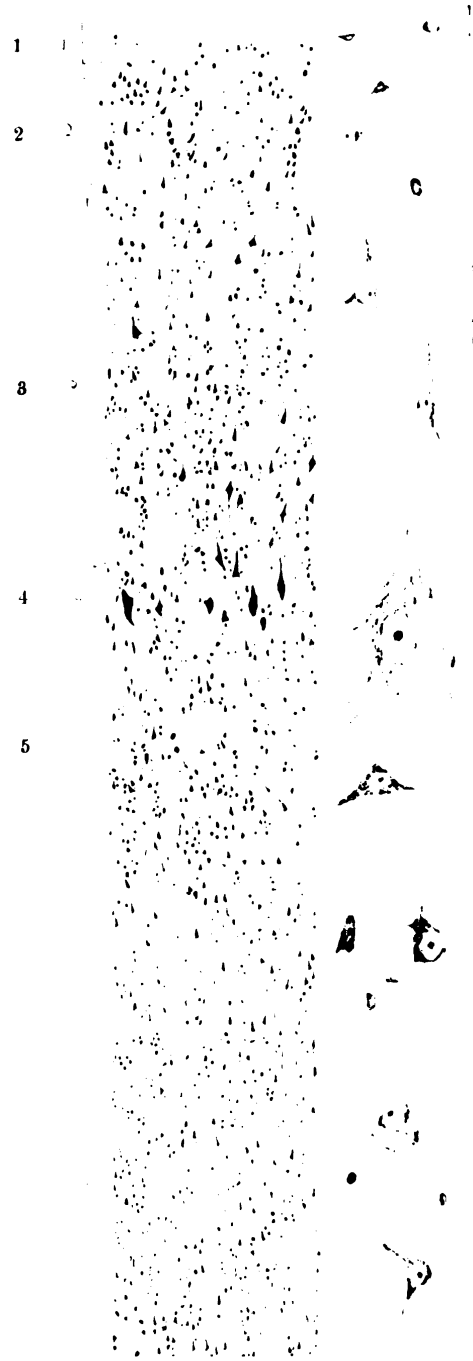


FIG. 2. Strip of epileptic imbecile brain, central region (Nissl).



PLATE IV.

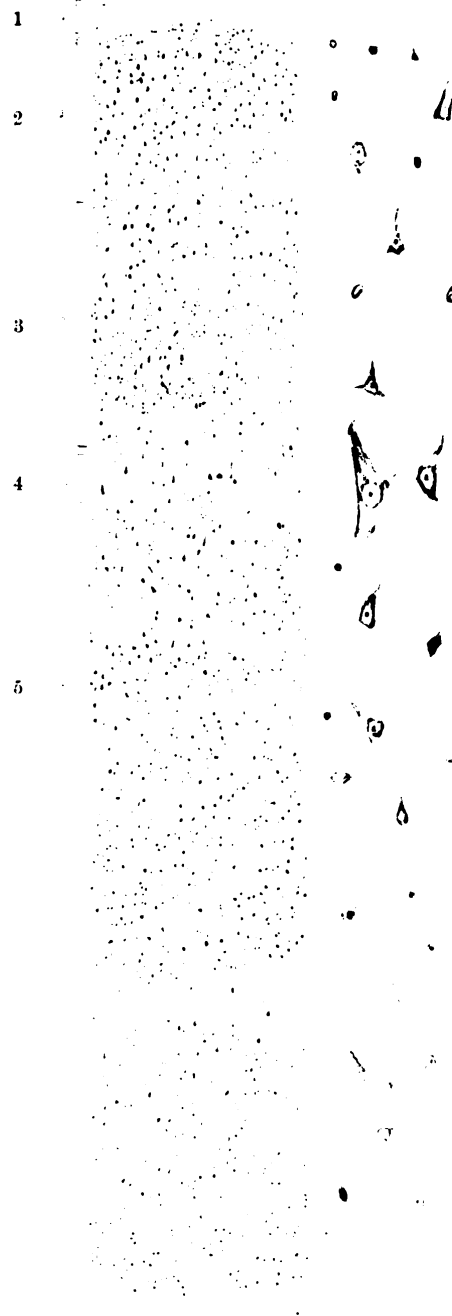


FIG. 1. Strip of infant's brain, central region (Nissl).





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PLATE V.



Cells from the sub-cortical layer of grey matter in the Heterotopic brain.  
 1. Stained by the Bielschowsky method for intracellular fibre.  
 2. Stained by Nissl method.



PLATE VI.

1

2

3

4

5

FIG. 1. Strip of normal brain, central region (Kulschitski-Pal).

*Enc. p. 293.*

1

2

3

4

5

FIG. 2. Strip of epileptic imbecile brain, central region (Kulschitski-Pal).

convolution, but on the mesial surface they extended to within 1 cm. of the callosal fissure. The largest cells of this type on the mesial surface measured 64 by 22, equal to about the average size Betz cell found in the lateral surface in normal brains.

The granular layer was of quite average development in all regions and the reduplication in the visuo-sensory area was well marked.

The cells in the sub-cortical layer were irregular in arrangement and distribution. As before stated, this layer was not visible to the naked eye as a grey area in the hippocampal or callosal gyri, but well-formed isolated cells were scattered between the fibres in these situations also. This layer formed a continuous deep belt of cells, but the lower edge of the belt was broken up into islands by bands of fibres.

No definite layers were discernible in this sub-cortical zone of cells. The cells lie at all angles, but a general view with the low power shows that there is a tendency on the whole for the apical process to point towards the cortex and the base inwards. The pyramidal type of cell predominates, but many polymorphic and immature cells are present. The apical process and axon are well marked, but the number of protoplasmic processes varies greatly; in some cases they are numerous and short, in others (bipolar or spindle-shaped cells) there are only two or three. Like the cortical cells proper they have large pale nuclei often occupying the greater part of the cell, and the cell body is flat and granular. Some of the larger pyramidal cells in this area show Nissl granules, as is seen in Plate V., 2; these cells were drawn from the sub-cortical region beneath the motor area.

The intracellular fibrillation, as shown by the Bielschowsky method, is poor, both in cortical and sub-cortical regions. In many cells the fibrils are only apparent in one part of the cell and, as shown in Plate V., some quite large cells contain only a few isolated fibrils. Still, the presence of these fibrils and of Nissl granules proves without doubt that the cells of the sub-cortical region were functionally active to some degree.

Herxheimer and Gierlich state that traces of intracellular fibrillation can be demonstrated in the brain of a six months' old foetus, but the cells of the motor area of the infant aged six weeks which was examined by this method failed to show any intracellular fibrillation, although a few extra cellular fibrils were present in that area.

The fibre layers of the cortex were incomplete in many instances, and the most noticeable feature of the sections was the deficiency of transverse fibres. This was most marked in the radial zone, as seen from the illustration (Fig. 2, Plate VI.). The sensory areas are better developed in this respect than the motor; in the visuo-sensory region

both outer and inner line of Baillarger are well marked and the tangential system generally is better developed than in the central region.

The resemblance of the type of cell and fibre in this cortex to that of the infantile brain is marked and some estimate of it can be formed from the illustrations. A large number of the cells of the cortex as well as those in the sub-cortical region are of embryonic type, and the development of intracellular fibrils is very defective. The fibres also, in their wavy margin and small calibre, resemble the defectively myelinated fibres of a developing brain (Plate VII., Figs. 2 and 3).

Besides the structural defects mentioned above there was some excess of neuroglial nuclei; the vessels were engorged and showed the dilation of perivascular lymphatics, which is common in epileptic brains. There was no indication, in any region, of old or recent inflammatory conditions, and no patches of sclerosis were found. Both uncinat regions appeared normal, and the structural defects described were the only noticeable abnormalities.

#### IV.

*Other cases of heterotopia.*—Virchow defined heterotopia of the cortex as grey matter occurring in positions normally occupied by other structures, and Anton, though stating that the most usual form is that of isolated areas of cells in the neighbourhood of the ventricular walls, mentions the occurrence of grey matter in the substance of the corona radiata, the cell elements of which comprise pyramidal and spindle cells as well as small round ganglion cells. The convolutions or cortex over these areas are, according to Anton, highly deformed or microgyric. Meine describes a case where macrogyria was present in the parietal region and the internal structure of that lobule consisted of grey matter for two-thirds of the distance from the external to the ventricular surface. In the superficial portion all the usual cortical layers were represented, but the deeper part, though containing cells of all varieties, was not differentiated into layers. This case, like several of the others reported, was accompanied by some meningitis. In his article Meine gives summary accounts of 13 cases reported by various writers up to that date (1897).

The cases vary in severity; one described by Ehrman having no psychic affection during life, yet showed extensive abnormal areas of grey matter in the walls of the lateral ventricle *post mortem*. Another case reported by Tungal only had mental affection after reaching the age of 31 years and about four weeks before death. Four other cases have been described which bear a considerable resemblance to the one with which we are dealing.

PLATE VII.



FIG. 1.  
Fibres from the inner line of Baillager. Normal.

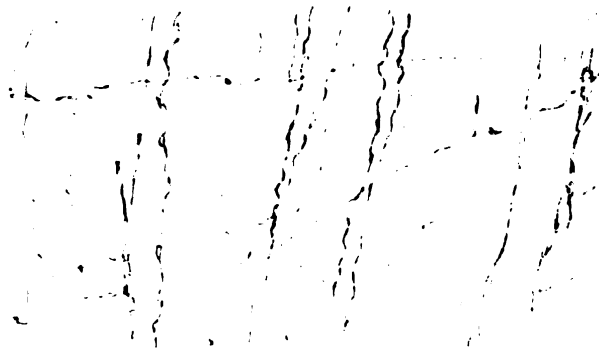


FIG. 2.  
Fibres from inner line of Baillager. Heterotopic brain.

FIG. 3.  
Fibres from sub-cortical region (central) Infant's brain.





Kolschitkowa reports a case of epileptic idiocy in a girl of six years of age in which the brain showed islands of grey matter in the medullary substance; the islands were composed of undifferentiated neuroblasts.

Winkler (Utrecht) describes the brain of an epileptic dement (aged 20 years) with a complete layer of sub-cortical cells,  $\frac{1}{2}$  c.m. broad, running parallel with the cortex from the frontal to the occipital region. This layer, which was not present in the temporal lobe, consisted of polymorphic and pear-shaped "ganglion" cells often of an embryonic type. There was some chronic inflammation of the pia.

Matell gives a full account of a female epileptic imbecile dying at the age of 25 years who, both in history and cerebral conformation closely resembles the case we have described. Not only does the sub-cortical layer of cells occupy very much the same extent and position, but Matell notes a deficiency in pyramidal cells of the superficial cortex, and mentions that the polymorphic layer is continued down into the subcortical medullary substance.

The fourth case, reported by Tedeschi, is that of a child, also an epileptic, with a brain of similar structure although the occipital region appears to have been less well developed than in our case. This writer notes the diminution in size of the nerve fibres.

All four of the above cases were epileptic, and, according to Anton, the condition of heterotopia is usually associated with epilepsy; but of the cases mentioned by Meine only five had fits, and these were cases having fairly extensive cell areas in some part of the corona radiata; the remainder of the cases had abnormal islands of grey matter in the region of the walls of the ventricles and were either unaffected mentally or subjects of insanity occurring in later life. In some of the epileptic cases the fibres are noted as being of deficient calibre and in most the cells or cortical development are described as embryonic. As suggested by Roncoroni, and ably supported by the investigations of Dr. J. Turner in this country, a persistence of subcortical cells (they were found present in a greater or less degree in from 70 to 80 per cent. of epileptics), together with other infantile characters, are the most constant structural defects in the epileptic brain. When we consider how slight a condition of toxæmia is sufficient to cause convulsions in infants it is easy to understand that, should embryonic or infantile features persist throughout life, a similar susceptibility to fits would also continue from causes insufficient to give rise to more than a passing indisposition in adults.

## V.

*Conclusions.*—It would appear then from the above account that this case, while conforming to Virchow's definition of heterotopia of the

cortex is in fact a mal-development, of which slighter degrees are not uncommon in the brains of epileptics. In other words, it is a persistence of sub-cortical nerve cells in a high degree, these cells having matured to the extent of exhibiting many functional characteristics. Whether this persistence and maturation is due to a compensatory effort on the part of the organ to supply the defect in the number of cortical cells which must have resulted from the elementary state of the fissures, or whether it is part of a general under-development, it is impossible to say. The defective myelination of the nerve fibres and poverty of intracellular fibrils shows the widespread and complete infantile condition of the neurons, and this under-development of fibres, though secondary to the cellular condition, may in part account for the position which the cells retain, since thick healthy fibres would necessarily tend to displace cell structures in the sub-cortical regions. It is, I think, clear that this case should be put in a different category from those in which isolated areas appear in the walls of the ventricle; the occurrence of the latter in otherwise normal brains shows that, though they may be developmental anomalies, possibly reduplication of lenticular, caudate, or amygdaloid nuclei, which we know to be of similar origin to the cortex, there may be no marked under-development of neurons in these cases and they are not necessarily accompanied by epilepsy or deficient mental capacity.

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## A PRELIMINARY NOTE ON BRAIN WEIGHTS AND MEASUREMENTS IN THE INSANE.

BY HELEN G. STEWART. M.D.

THE relation of normal brain weight to body weight was worked out by Marshall from data collected by R. Boyd, and efforts have been made at various times to correlate brain weight and mental deficiency or mental perversion. The indifferent success of these efforts is not a matter for wonder when we consider the various factors which may contribute to alter the relative brain weight apart from the normal development of nerve cells and fibres. Nevertheless the low type of some of the brains seen at asylum *post-mortems* is a striking feature and is not confined to a low weight as compared with the body weight. In the following inquiry, which was suggested by Dr. Mott, the relation of the weight of the cerebral hemispheres to that of the combined pons, medulla, and cerebellum (normally 8 to 1) has been considered as well as several other factors.

In all, the results of the notes in 167 cases have been analysed, and the features which have been taken as indicating a congenitally low type of brain or an unequal development predisposing to insanity are:—

(i.) A brain weight markedly below the average healthy weight for the same age, body weight, and height. For this purpose the weight of the whole brain was taken, together with the membranes *in situ*.

(ii.) A disproportionately low weight of cerebrum as compared with the united weight of pons, medulla and cerebellum. In this case the loss of weight from wasting, as evidenced by thickening of the membranes and excess of cerebrospinal fluid was taken into consideration.

(iii.) A poor development of the higher (association) areas, as shown by:—

(a) Shallowness of the fissures.

(b) Poverty of secondary markings on the convolutions.

(c) Flattening and poor development (and therefore diminished size to measurement) of lobules, especially in the frontal and parietal areas.

(d) The extension of some areas beyond their normal position, *e.g.*, the extension of the striate area on to the parietal surface as indicating a measure of poor parietal development.

A brain tissue has been considered to be of low type if the condition in (iii.) co-exists with either (i.) or (ii.). If the features given in (iii.)

occur alone the brain has been considered ? low type. Working on this basis it was found that 32 in 84, or 39.2 per cent., of the male brains were of undoubted low type, while 11 in 84, or 13 per cent. were of ? low type. In female brains 28 in 82, or 34.1 per cent., were of low type, and 16 in 84, or 19.5 per cent. of ? low type. Thus, taking male and female together, 36.65 per cent. of the certified insane dying at Claybury possessed brains of a low type, and if to this number the 16 per cent. ? low type be added, the percentage amounts to 52.3 of the total insane.\*

In this connection, it is interesting to note that of four cases of tumour of the brain three show the conditions mentioned in paragraph (iii.), and in the fourth case no particulars were given. Since in a normal brain the occurrence of a cerebral tumour causes certain definite symptoms, while in cases of tumour of the brain which are admitted to asylums insanity is often the only prominent feature, it seems probable that in the latter cases the brain is inherently liable to insanity, and any disturbance of the normal equilibrium is sufficient to cause the onset of symptoms. In the three cases mentioned above the tumours differed greatly in position and size. One, occurring in the calamus scriptorius of the fourth ventricle, measured 2 cm. in length; a second was in the region of the pituitary body, and had a diameter of about 4 cm.; the third occupied the left frontal lobe, and extended from the anterior pole of the hemisphere to the level of the anterior horn of the lateral ventricle. Thus it appears that the factor causing insanity in these cases is neither the position nor the size of the tumour, but is, probably, a condition common to all three of the brains mentioned, *i.e.*, a low type of development—as an inherent defect.

The following tables show the relation of the weights of the “insane” brain—of “ordinary type” and “low type” respectively—to those of the brains of healthy persons of the same age and height. The tables for normal brains are taken from Quain’s “Anatomy of the Brain.” In the case of the figures bracketed only one brain of that age and height occurred in that class, hence no conclusion can be drawn. These figures show clearly that brains possessing the features mentioned in paragraph (iii.), and called “low type,” have a lower average weight for the same height and age than brains of either the rest of the insane or the healthy type.

\* Since accurate measurements have been taken in all brains (*i.e.*, the last 46 cases considered above) the percentage has been found to be considerably higher. In the males, 10 in 21, or 48 per cent., were low type, and 4 in 21, or 18 per cent., of ? low type. Among the females, 14 in 25, or 56 per cent., were low type, and 6 in 25, or 24 per cent., of ? low type. If these figures be taken together it gives 80 per cent. females and 66 per cent. males of a low type, or a total of 73 per cent.

## TABLES.

Average relation of Brain weights of Sane and Insane of normal and low type, arranged according to age and height.

## FEMALE BRAINS (82 CASES).

## I.—SANE (Quain's "Anatomy").

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.62 metres and over ...	1245	1209	1166
1.54 " to 1.62 metres ...	1218	1211	1129
1.52 " and under ...	1198	1204	1112

## II.—INSANE (not low type).

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.62 metres and over ...	1268	1221	1160
1.54 " to 1.62 metres ...	1325	1213	1100
1.52 " and under ...	—	1272	—

## III.—INSANE (low type).

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.62 metres and over ...	1163	1168	1191
1.54 " to 1.62 metres ...	1125	1177	1056
1.52 " and under ...	(1260)	1127	(970)

## MALES (84 CASES).

## I.—SANE.

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.72 metres and over ...	1409	1364	1329
1.67 " to 1.72 metres ...	1360	1334	1304
1.65 " and under ...	1331	1296	1251

## II.—INSANE (not low type).

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.72 metres and over ...	1466	1371	1322
1.67 " to 1.72 metres ...	1297	1376	(1400)
1.65 " and under ...	(1080)	1309	1267

## III.—INSANE (low type).

	20-40 YRS.	40-70 YRS.	70-90 YRS.
1.72 metres and over ...	1357	1321	1117
1.67 " to 1.72 metres ...	1186	(1057)	(1062)
1.65 " and under ...	1199	—	—

Nevertheless, it is not contended that all, or even any, of the features mentioned above, are peculiar to the brains of the insane. Many of the patients were not imbecile, and hence sane in the eyes of the law until their certification at various ages. Therefore, we must believe that numerous brains of this type do not enter asylums, and are to be found in the P. M. room of any hospital. But the large proportion of brains with features indicating a low type of development among asylum patients suggests that such individuals are more subject to a disturbance of the mental equilibrium than members of the community who possess brains of the average type.

## SOME OBSERVATIONS ON A CASE WITH IMPULSIVE OBSESSIONS OF SUICIDE AND AUTO-MUTILATION.

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London County Asylum, Long Grove.

THOUGH the literature in connection with abnormal impulses is already so extensive, the following case seems worthy of record, as it presents several features of interest.

The psychological mechanism which produces such striking modification of the fundamental human instincts, as impulses to suicide and self-mutilation, is often extremely complex and difficult to interpret. In one group of cases they are manifestly secondary to an insane mental state, of which, indeed, they are only the logical outcome. Under this category come states of depression or some form of hallucinosis, where the sensory promptings are often endowed with strong impulsive force. In another group the impulse is carried into execution in a state of more or less unconsciousness, with subsequent amnesia. The impulses of epilepsy, acute alcoholism and hysteria are frequently of this type. The origin of the impulses becomes much more obscure when they form the most obvious feature of the psychosis and are carried out in a state of complete consciousness, with the intellect unimpaired and the patient recognising the irrational character of his actions.

There are no general principles which adequately explain all the cases comprised in this group, and, indeed, the impulses would sometimes seem to result from some unknown perversion of the normal instinct of self-preservation.

Mrs. W. was transferred to the Long Grove Asylum on October 28th, 1907, having been originally certified in January, 1902. Her age is 55. She is of medium build and weight. Some slight facial asymmetry is noticeable, and the palpebral fissures slope slightly upwards and outwards. These features give the expression a somewhat unpleasant cast. Physical examination reveals signs of mitral and aortic disease and thickening of the right pleura. These lesions are well compensated and she is otherwise strong and in moderate health. As regards her general mental characteristics she is a quiet, reticent and somewhat self-engrossed woman. She is not, however, actually unsociable, and she establishes herself on terms of friendship with some of her fellow patients. She is, however,

sensitive and easily upset, but shows very little outward signs of such feelings, becoming, when in any way annoyed, quieter and more reticent. She is very industrious and obliging. The intelligence is about the average, and there is no evidence of any delusional ideas. Owing to the fact that she looks on herself as an undesirable member of her family, she has for many years ceased all communication with them. Her memory is, however, ready and faithful, so that although the history which follows is mainly a personal one, there is no reason to doubt its accuracy. Any of her statements which it has been possible to verify from independent sources coincide identically with her own.

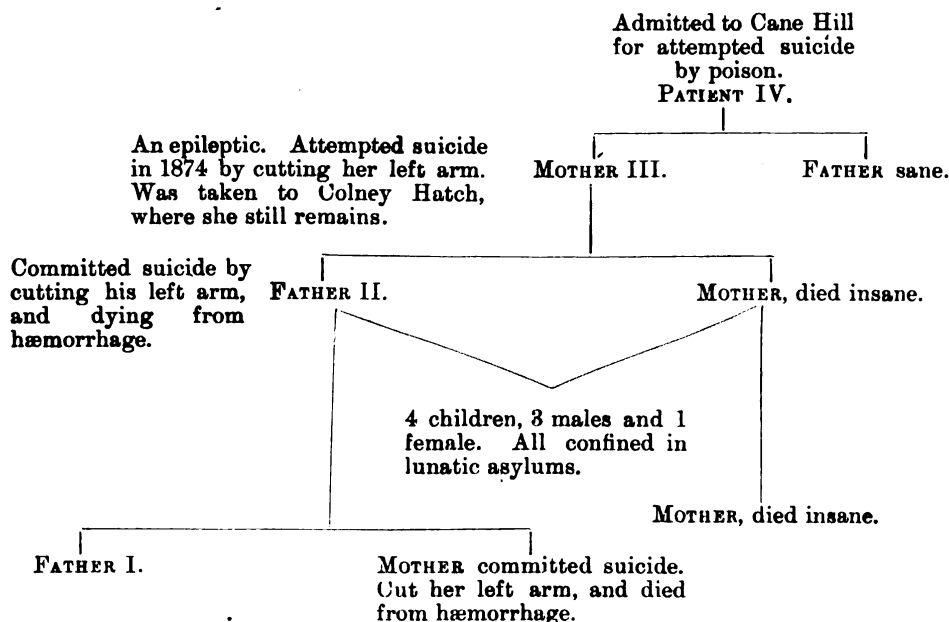
The *family history* is as follows: As far as she knows the grandparents on the mother's side died of senility and showed no neuropathic tendencies. On her father's side she knows nothing of them; one of his sisters died of phthisis and the other went to Australia and has not been heard of since. Her father himself was extremely passionate and gave way to bouts of excessive drinking. Her mother committed suicide, as also did one of her sisters. Her two other aunts were apparently normal mentally.

The children of this union were nine in number. The patient herself is the fifth child and has strong suicidal tendencies. Her younger brother committed suicide for some trivial reason; one sister was hysterical. The other children displayed no abnormal tendencies, two dying of fever in adolescence.

In spite of many gaps and imperfections in this history, it is of considerable interest, for we find an alcoholic father (? dipsomania) and three suicides in the two generations with a potential case in the patient herself. She has not seen her relatives for some years, and it is quite possible that there may now be further manifestations of this neuropathic heredity. Unfortunately this cannot be investigated. The incidence of suicides is especially noteworthy. Heredity seems to exercise a particularly strong influence in the production of this particular impulsion, and numerous remarkable examples are recorded. Bucknill and Tuke quote a case of Falret's, where four brothers in a family of six attempted suicide (1). Two of them, in addition to a cousin, accomplished the act. Morel mentions an instance where seven brothers destroyed themselves, though in good position and suffering from no misfortune (2). In these cases, no doubt, imitation and suggestion play a large part. Analogous are instances of collective suicides and *suicide à deux*. These factors are, however, probably only operative given a primary neuropathic predisposition.

In his presidential address at Leicester, in 1905, Dr. Mott gives a striking instance of four generations of suicide (14). The result of imitative suggestion on a neuropathic stock is in this case especially well illustrated, for one sees that precisely the same method of accomplishing the suicidal act was adopted in three consecutive instances.

This will be clear from Dr. Mott's diagram:—



The early history of Mrs. W. is as follows:—

Up to the age of nine her life was uneventful. She was delicate, and her education was somewhat deficient for that reason. At this period her aunt paid a visit to her mother and told her that she had been suffering very much from pains in the head, adding "I don't expect you will ever see me again." The next day the news came that she had committed suicide by taking poison. The information impressed the patient curiously. Instead of feeling very shocked, she thought what a pleasant form of death it was, and how nice it would be to die in a similar way.

From this notion she was unable to rid herself. It became a veritable obsession, and made her life very miserable. The idea shortly afterwards acquired impulsive force and she swallowed some white precipitate. Prompt treatment averted serious consequences. Not long after she was discovered by her mother kneeling down by the bed, holding an open razor and praying that she might have strength to destroy herself. She had already inflicted a slight cut. At the age of 14 she was sent to service. One day, while cleaning a grate, she suddenly threw down the brushes, rushed across the road and jumped into the sea. This, she says, was quite a sudden and unpremeditated impulse, and is quite inexplicable to her. She was rescued and sent to a "home of correction" for 12 months. Upon her release the same feelings and ideas obsessed her. She became restless and uneasy, and was unable to settle to anything. Having obtained some laudanum she was again nearly successful in taking her life. On this occasion the doctors said she had swallowed enough to "kill a horse."



More or less serious attempts at suicide in children are not uncommon. Janet mentions several cases, one in a girl eight years old (3). For three years she had only had one idea in her head—that of dying. She was constantly talking about it and made various preparations for carrying her ideas into execution. The origin of the obsession was quite obscure. In other cases described some trivial motive provoked the act—punishment for a fault or some trifling humiliation. Such a reaction is, however, always indicative of profound nervous instability, usually hereditary. In the present instance the origin of the idea is more or less evident, dating, as it did, from her aunt's suicide.

At the early age of 16 she married, and for many years lived more or less happily. She had no family. She was still, however, convinced that she was fated to die by her own hands and was constantly obsessed by the desire to accomplish the act.

These feelings were always aggravated by any trifling upset, and then the impulse was with difficulty controlled. She describes how sometimes she would walk for miles to remove herself from temptation, often, however, going so far as to purchase poison. Sometimes there seem to have been actual attempts, but none very serious. She remarks that it is a mystery to herself why she never succeeded.

The last few years of her married life were unhappy ones; her husband was intemperate and treated her badly. At the age of 40 she was going to Brighton with her husband on a visit to her mother; on the way he told her not to be surprised if she found her mother was dead. Upon her arrival she discovered that her mother had recently cut her throat and that a few months previously her brother had hanged himself. No cause was assigned for the mother's action, and her brother had apparently had some difference with his wife. This news seems to have reduced her to a state of desperation, and she felt indifferent to anything which might happen. She confesses to some excess in alcohol and that she quarrelled fiercely with her husband. Shortly afterwards she set fire to their house and delivered herself up to the police, telling them that her intention was to destroy her husband. She now says, however, that she was in a state of frenzy and did not really appreciate what she was doing. She was sentenced to 12 months' imprisonment for arson; while in prison she tried to starve herself and was reduced to a state of emaciation. Upon her release she went to live with a brother and separated herself from her husband. Eventually she obtained employment in an hotel. She mentions one or two occasions during this period when she purchased poison with suicidal intentions. In January, 1902, she went to the Infirmary suffering from tonsillitis, and was transferred from there to the Cane Hill Asylum, the certificate stating that she was depressed and threatening suicide.

Dr. Moody has very kindly furnished details of her conduct in the asylum. The following are the salient features:—

She was very depressed on admission and remorseful over "acts she can never undo." She was morose and reticent, and usually sleepless, but had much improved by May of the same year, when she again relapsed, refused her food and

had to be fed mechanically. She heard voices telling her to die, and she had marked ideas of unworthiness. During the year she had frequent relapses of this kind, in the interval, however, giving no trouble and working industriously. In May, 1902, she smashed three windows without any warning, explaining subsequently that the "devil was inside her" and she "wanted to see the blood fly." From this date she was subject to paroxysms of impulsiveness, and frequently inflicted more or less serious injuries on herself. She was transferred to Hellingly on March 18th, 1904.

The following particulars of the patient were kindly supplied by Dr. Taylor, the Superintendent of Hellingly Asylum:—

On admission she is described as being dull and perplexed, constantly rubbing and looking at her hands, and only expressing herself in a disconnected way. "I am quite well and not afraid; smashed 15 windows in Cane Hill; I liked to be covered with blood sometimes. It isn't that I hated the place. I've never been the same since poor mother died; she killed herself; cut her head off; did it with a razor. They all die like that. I never should, though; I'm too big a coward. I like myself too much for that."

She soon improved, though frequently irritable and bad tempered, but showed from time to time extreme impulsiveness. An eye-witness describes how she would suddenly jump up and either smash windows or crockery, explaining that she liked to feel "wet blood." Towards the latter part of her time in the asylum she became more cheerful and less impulsive, and was transferred to the Long Grove Asylum on October 28th, 1907.

Since her transfer the following particulars have been noted:—

During the time she has been under personal observation there have been no severe impulsive outbursts, though she still has similar tendencies which are fortunately less serious in their consequences. There have been no attempts at suicide, though she still retains a fatalistic belief that she will die by her own hands. The most obvious abnormality which she exhibits is a craving to inflict wounds upon herself. As she shows more or less anxiety for discharge, she makes a superficial attempt to conceal her strange propensity and frequently says: "But I'm all right now; perhaps I may never want to do anything like that again. I am quite able to go right away." She cannot, however, hide the fact that she has a constant craving for the sight of her own blood. Though she tries to make light of it and adopts a callous tone when talking on the subject, she quite realizes that such a craving is unnatural and abnormal, and adopts various precautions against yielding to the impulse. Thus she sits in a remote corner of the room as far away from the windows as possible, because they are such a source of temptation to her. They sometimes arouse in her such an irresistible impulsion to smash, that she is forced to walk away from them or cover up her eyes with her apron. She finds that constant employment is the best means of diverting her attention from the craving, and always occupies herself most industriously.

Periodical states of depression are noticeable, when she becomes rather irritable and more reticent. At these times she broods over former acts of delinquency and thinks how wicked she has been. Life becomes almost intolerable to her, and she

feels that the routine of her daily existence cannot be endured any longer. The craving to wound herself, at such times, becomes an imperative necessity. Her sleep becomes disturbed, and if she should drop off for a few minutes she has unpleasant dreams in which she pictures herself smashing and covered with blood.\* Having at length yielded to the impulse, these depressing feelings vanish and she experiences a sense of great relief.

This sequence of events has occurred several times while she has been under observation. Usually she is content with inflicting trivial abrasions on her skin. She tries to conceal them, but does not deny that they were purposely produced when they are discovered. She generally tries to turn the subject or smiles and says: "Oh, that's nothing. I feel better now. It's nothing to what I used to do!" On one occasion she picked up a bit of glass and inflicted a more severe gash on her arm. She was very upset when the incident was reported to me, and was unwilling to have the arm examined. Eventually she confessed that someone had spoken unkindly to her and this had produced feelings of depression. She had discovered the glass accidentally and had immediately sought relief by cutting herself.

Her more general mental state has already been described.

The above history reveals the fact that for many years the act of suicide and latterly self-mutilation have possessed for Mrs. W. a peculiar attraction.

Though she tries to restrain these strange cravings, knows they are abnormal, and adopts various precautions against carrying them into execution, yet she makes it clear that the ideas in themselves are not repugnant to her, and that she has always experienced gratification and relief when she has to some extent yielded to them.

The question which arises is, what significance must be attached to such evident moral perversion as the patient displays? Do these unnatural cravings indicate that the patient has inherited tendencies which are fundamental and instinctive in her though repugnant to the instincts of the normal individual? Her general mental attitude towards these ideas, and the fact that she developed suicidal tendencies while very young, seems to almost indicate that such is the case.

An endeavour will be made to show, however, that her cravings are purely accidental in origin and imply no original and inherent moral defect, differing only from the ordinary harmless obsessions in their particularly unpleasant content and the impulsive force with which they are at times endowed.

\* This is an interesting example of a dream mechanism described by Freud in his "Traumdeutung" (4). In the waking state we have a conflict of two systems of emotionally toned ideas or, as they are termed, "complexes." In the present case these are the obsessive impulse to draw blood, and the total system of motives and ideas of the personality which endeavours to repress this desire. During sleep the personality loses its co-ordinating force and the suppressed complexes tend to run riot. Hence it is common in dreams to find the suppressed desired fulfilling themselves. This has occurred in the present case. It is more usual, however, for the complex to express itself symbolically rather than directly. (See also Jung (4).)

In the first place it is easy to demonstrate that the instinct of self-preservation is as strong in Mrs. W. as any one else.

When she suffers from cardiac pain or has some œdema of the feet owing to her heart lesion, she is very worried and grieved, willingly taking any advice which may be given to promote her recovery.

It is evident, therefore, that she does not really want to die or suffer pain more than any one else, though at the same time she will say that the idea of suicide is neither repugnant nor unpleasant to her.

Again, though obsessed for many years by the craving to take her own life she has never succeeded in completely accomplishing the act. Many writers have noticed that suicidal obsessions are usually more theoretical than impulsive. The question is a large one, and is fully discussed in Janet's "Obsessions" (6). Though in the present case the patient's impulses have been numerous and serious in their results, yet it is extremely significant that she has never actually gone so far as to take her own life. Apart from other considerations which might be discussed in regard to this point, one is justified in assuming that the instinct of self-preservation has been sufficiently strong to prevent her from completely yielding to the impulse which is so imperative. As she herself says: "I am too much of a coward. I'm too fond of life."

Paradoxical as such a state of mind appears to be, it seems as if it is not so much a wish to die which has obsessed her but the particular act of suicide, which exercises such a peculiar fascination.

The condition is analogous to that of the dipsomaniac, who has no wish to become drunk, but has acquired a tendency which he is unable to resist and which at times becomes an imperative necessity of his existence.

This curious attitude is well shown by her statements in regard to one of the occasions when she was trying to starve herself. She said that though the pangs of hunger were very severe they were far outweighed by the *pleasure* she experienced at yielding to her craving for suicide.

It is now necessary to notice more particularly the conditions under which the suicidal obsession originated.

How far external events which produce a strong emotional reaction are instrumental in the production of fixed ideas is a matter of considerable dispute. Even those writers who consider that psychic trauma is the necessary antecedent of an obsession demonstrate that the fixed idea itself is not usually the original idea associated with the painful emotion, but one which is substituted for it. The emotion remains unchanged and attaches itself to an apparently irrelevant (defensive) idea which constitutes the obsession (7).

In this particular case, however, not only is one justified in assuming

that the obsession owed its origin to a very definite moral shock (news of her aunt's death) which the patient experienced, but also it is to be noticed that the content of the obsessions is immediately related to the event which provoked it.

Such an obsession is called by Freud "traumatic," and is distinguished by him as a class apart from the usual type. He says it is an intense obsession which is nothing else than the memories—the unaltered images of important events (8).

Janet also mentions that it is possible for some isolated moral shock to determine the origin of an obsession and its peculiar content (9).

Krafft Ebing may also be quoted when he says: "A fixed idea may come into consciousness suddenly or is called up by some violent external event (suicide of friend). The content in the latter case (*i.e.*, perceptual) consists of the continued activity of apperception with reference to the original distressing thought" (10).

It will be remembered that when the patient was informed of the tragic death of her aunt she re-acted very abnormally. The most natural and adequate reaction would have been the ordinary manifestation of grief in a child, *viz.*, a fit of crying.

If this had occurred the emotion would have been "worked out" and the ideas bereft of their *affect* would have been forgotten in the process of time.

Instead of this a very different sequence of events occurred. Among other painful associations aroused was a not unpleasant one that such a death was easy and attractive. Such an idea might, of course, occur to any one and in itself implies no defect of moral sense. The abnormality lies in the fact that it assumed a pathogenic character and remained as an insistent obsession. The explanation of this may be that the idea was here a "defensive" one, and remained fixed by the emotion which failed to find expression in the ordinary way.\* Whatever be the exact mechanism of its occurrence it is clear that from this time, as she herself says, she could not rid herself of the idea of suicide and henceforth became miserable, depressed and morose from the craving to follow her aunt's example.

This obsession has now become to the patient no more than a theoretical belief that she will die by her own hands, as so many of her family have done. It has been replaced by a craving to wound herself. When she "smashes" she says she has no idea of taking her own life

\* The word "defensive" is here used in the sense that the idea was effective in protecting the personality against the painful complex which must be aroused by a moral shock such as the patient experienced. This complex was "suppressed" by the protective idea instead of being normally expressed by the usual emotional outbursts.

and neither does she wish to needlessly destroy the property of the institution. Being a well-disposed woman she regrets giving trouble, but says she really cannot help herself from smashing at times, because she craves so much to see the blood flowing from the wounds which she inflicts.

The craving arose quite accidentally. She was at Cane Hill at the time passing through a phase of considerable depression. Shortly before she had been fed mechanically owing to refusal of food. She had become obsessed by ideas as to her own wickedness and felt quite unable to shake off her depressing thoughts; existence became so unbearable to her that she felt the imperative necessity of doing something desperate to "relieve her feelings." She says she seemed to be "dominated by the devil" and something inside her appeared to be telling her to smash. (These sensory disturbances probably come under the category of pseudo hallucinations. They did not have for her the attribute of objective reality and would seem to be the symbolic expressions of her compulsive feelings.)

In this state of mind she suddenly and for the first time smashed several panes of glass, inflicting several cuts on her arm; this was successful in relieving her depression and she experienced a feeling of relief and satisfaction. The patient's action is quite comprehensible, and one finds analogous examples in normal life where persons attempt to suppress painful feelings by violent and sometimes irrational methods of distraction. The interesting feature is that from this time the craving to wound herself commenced to obsess her. She knows her craving is absurd and irrational, yet at times it becomes irresistible. What had happened is, that the painful complex of unworthiness had been suppressed by this unnatural impulse, which thus became an act of defence against the ideas which caused her so much anguish.

This particular mechanism in the origin of impulses is described by Freud in the following words (11): "The primary idea . . . is replaced by acts or impulses which have served originally as methods of relief or protection, and which now find themselves in grotesque association with an emotive state which does not belong to them, but which has remained unaltered." An illustrative example may be quoted: "Obsession of arithmonomania.—A woman has contracted the habit of always counting the boards of the floor, the steps of the staircase, etc., which she does in a state of absurd distress. She had commenced to count to distract herself from the obsessing ideas (of temptation). In that she was successful, but the obsession to count has taken the place of the original obsession."

In a paper on impulses, some of which closely correspond to those observed in Mrs. W., Janet gives a somewhat similar explanation as to

their particular rôle in relieving the crisis of psychasthenia (12). He says: "These absurd acts are passionately sought for simply because they are exciting acts, and these individuals have an urgent need of excitation on account of the anguish which the mental depression produces." This point of view is well illustrated by the present case. It will be remembered that the patient from time to time became very depressed and miserable. She felt unable to concentrate her attention on anything, realised the hopelessness of her position, and became generally irritable and out of touch with her environment. Sometimes these crises appeared to be due to some exciting cause, *e.g.*, a slight rebuff or the death of a fellow patient to whom she was attached. The latter incident produced a very marked psychasthenic state. She was obsessed by ideas that she must be different from everyone else, and that anyone who came into contact with her seemed to be dogged by misfortune and trouble, etc. At other times these crises appeared for no apparent external cause. It was always on such occasions that the craving became uncontrollable and she felt the imperative necessity for wounding herself.

Thus far an attempt has been made to show that the unnatural impulses displayed by Mrs. W. were not instinctive in her, but were accidental in origin, the result of certain emotional experiences.

Seeing that suicide was relatively common in her family the question arises as to what part this neuropathic tendency played in the production of a similar impulsion in the patient herself. The answer seems to be that the suicidal impulse was transmitted in the same way as one sees alcoholism occurring in successive generations of the same family. Bevan Lewis (13) has recently pointed out in a paper on the subject that in no sense can alcoholism be spoken of as inheritable, *i.e.*, alcoholism as a specific character.

He says "what is transmitted by an alcoholic ancestry is a defective organisation of the neuron, revealing itself in a loss or weakening of that primary attribute so characteristic of nervous mechanism—inhibition." Such an observation applies equally well to the case of Mrs. W. One sees a very striking example of a bilateral neuropathic heredity in the production of a congenitally weak mental organisation.

The hereditary instability is the condition which has been transmitted. It finds expression in abnormal modes of reaction in times of stress, the occurrence of unnatural cravings and obsessions, periodical crises of depression, and states of defective inhibition. The peculiar content of the obsessions must be ascribed to the nature of the event which has provoked it. Education, environment and psychic trauma, especially in the suggestible period of early life, may either modify or produce abnormal mental tendencies, but one must assume that, from the first, in

that class of case coming under the general category of "psychic degeneration" there exists a badly endowed nervous organisation which forms the soil for the development of the various types of neurosis.

What specific causes make one individual an hysteric, another a paranoiac, and another a psychasthenic are at present imperfectly understood.

In conclusion, I must express my indebtedness to Dr. Bond for permission to publish this case, and also for his assistance both in obtaining facts as to her previous history and in making suggestions in regard to some of the points of interest.

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A SHORT ACCOUNT OF THE INCIDENCE OF DYSENTERY  
AT LONG GROVE ASYLUM FROM ITS OPENING  
(JUNE 18TH, 1907), TO OCTOBER 31ST, 1908.

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Much has been written during recent years, both in these archives and elsewhere, on "asylum colitis," or dysentery, and there appears but little excuse for increasing the literature upon the subject, save from one who can throw further light upon the ætiology of the disease in its widely different forms.

No such work has been done on this disease at Long Grove, but we have unfortunately been favoured with a very large number of cases, and as a careful record has been kept of these from the opening of the institution, Dr. Mott suggested that a summary of our cases, their ward-to-ward transfers, with a few notes and observations on our experiences, might be of value.

There is now but little room to doubt that asylum dysentery is one of the infective diseases caused by a specific organism, the isolation of which appears to be very difficult, and bacteriologists are not yet agreed as to its exact nature.

Our ignorance of the life history of the organism causing the disease adds greatly to the difficulty of efficient disinfection, isolation, treatment, &c. The incubation period of the disease, why or by what conjunction of circumstances it appears in such widely differing clinical forms, whether the stools alone are infective, and the duration of infectivity after the disappearance of symptoms, are questions which still await definite answers.

The period with which this paper deals extends from the opening of the Asylum, June 18th, 1907, to the end of October, 1908, during which time over 2,500 cases were admitted. The great majority of the early admissions were transfers from other asylums, and most of them had been insane for many years. In cases of all transfers enquiry forms were sent, asking (amongst other questions), whether the patients, during their sojourn at the asylum, had had any diarrhœcal or dysenteric attacks, so that we had some record of all our transferred patients in this respect. But, as the Tables at the end of this paper show, in only

one case was there a record of previous dysentery and one of "simple diarrhœa."

The method adopted in dealing with the disease has been uniform throughout; that is, immediate isolation of all suspicious cases, disinfection of all clothing, &c., with which the patient had come into contact, and nursing and sanitary precautions, as in cases of enteric fever. It is interesting here to note that during the period under discussion three cases of enteric fever have occurred. One evidently contracted his infection prior to admission, and in the other two no source of infection could be ascertained, but they occurred in different parts of the asylum and at considerable intervals. The diagnosis in each case was confirmed by the Widal reaction: two proved fatal and the third was subsequently discharged recovered. In none of these cases did the disease spread, but, during the same period, although similar precautions have been taken, we have had 80 cases of dysentery. On the male side all suspicious cases were isolated in J.1 infirmary until the opening of the sanatorium in June, 1908, as a dysentery villa; on the female side F.1 infirmary has been used throughout.

Typical and severe cases of dysentery are easily recognised, but even here some time must often elapse before a certain diagnosis can be arrived at, as the general symptoms of an acute infective disorder often precede those pointing to disease of the bowel by a considerable number of hours; indeed, it is no uncommon occurrence for a patient to complain of constipation at the commencement of the attack. A large preliminary dose of castor-oil is helpful both as a method of diagnosis and treatment.

The mild, atypical, and abortive cases are very difficult to discover, and there is not the least doubt that many of them are reported as cases of simple diarrhœa, and probably as many more are never discovered at all and get well without any form of treatment. Several of our cases were discovered quite accidentally. Two of them were patients who slept in single rooms and the diagnosis was made by the discovery of blood and mucus in the chambers which they used. These two patients made no complaint, there were no constitutional symptoms, the motions were not frequent, and, after being transferred to the isolation ward, no further abnormal motions were passed. Had these patients been sleeping in a dormitory and had access to a water-closet instead of being obliged to use their chambers, it is probable their attacks would have passed unnoticed. In another case, a sensible patient, whose statement might be relied upon, complained to the doctor that, instead of the constipation with which he was usually troubled, he had for the last few days suffered from diarrhœa, and his motions contained blood. The next motion was saved, and was diagnostic of dysentery: the patient had a

somewhat severe attack, but much resented being sent to bed and placed on milk diet. This patient worked in the ward, and, both inside and out, had free access to the lavatories, and he had not complained to, or attracted the attention of the attendants.

Another patient stated that on several occasions during the last five years he had passed blood and slime for a day or two at a time: the first occasion being whilst he was an inmate of a large workhouse infirmary. He had not thought it worth while complaining to a doctor, more particularly as he disliked being transferred to an infirmary ward and going to bed. There seems no reason for doubting the truth of his story, and he had probably previously had several mild atypical attacks of dysentery.

The main building of the asylum consists of two stories. The wards are designated by letters: the ground floor being called "one," and the first floor "two." Thus, A.1 is on the ground floor, and A.2 directly above it. Besides the main building, which contains between 1,600 and 1,700 patients, there are eight villas, accommodating 400 patients.

A glance at the Tables will show that the great majority of the cases of dysentery arose in ground-floor wards of the main building.

The ground-floor wards contain nearly all the patients with defective habits, and of these wards B.1, C.1, D.1, F.1, on the female side, and H.1, J.1, K.1, N.1, O.1, R.1, on the male side, accommodate the most degraded population; indeed, a very large proportion of the patients in these wards are habitually wet and dirty. It will be seen that these wards yielded an overwhelming majority of our cases. The up-stair wards, the large "working" wards (S. and L.), and the villas, contain very few patients with defective habits, and they contributed but few cases of dysentery; moreover, cases occurring in these "clean" wards were invariably solitary, and, for obvious reasons, the infection had but little opportunity of spreading. On the other hand, when the disease arose in wards containing degraded patients, it was the exception to find that it was solitary, but as a rule small epidemics occurred or groups of cases developed the disease within a few days of one another. In the tabulated summary of the cases, I have arranged columns showing the mental state, the habits, the employment in which the patient was engaged, and what their general health was considered to be at the onset of the attack. The results are very striking—the majority of the patients were suffering from advanced dementia of some form, and were defective in their habits, but few employed themselves in any way and most of them were in feeble or only moderate physical health.

Have not these facts an important bearing on the epidemics of dysentery which are noted as being so common during the early life of a new asylum?

Dr. Mott, in numerous reports and publications on dysentery in asylums, points out the necessity of exercising great care in transferring old cases of dysentery to a new asylum. Dr. Stansfield, in a discussion of Dr. Mott's paper before the Epidemiological Society, attributes the early epidemics of dysentery at Bexley to patients transferred from other asylums suffering from a latent form of the disease. Dr. Taylor, the medical superintendent of the East Sussex Asylum, Hellingly, in his annual report for the year ending March, 1905, refers to the early outbreaks of dysentery in that asylum, and states that, in his opinion, the disease was imported from other asylums. He points out that dysentery is a disease which is constantly liable to relapse, and draws attention to the great difficulty in diagnosing the mild and atypical cases. Dr. Candler, in his paper on dysentery in the Archives of Neurology, Vol. III., gives numerous instances of the influence of transfers, both those from ward to ward in the same asylum and those from one asylum to another.

All of these authorities appear to be in agreement upon one important point, namely, that some of the patients who have suffered from dysentery carry the infection for a long time afterwards. What proportion of patients remain infectious for a prolonged period or what the limits of this period may be there is no evidence to show, but there is little doubt that in some cases it extends to many months or even years. In the light of these facts one can scarcely be surprised when Dr. Mott hints that, to prevent an epidemic of dysentery at a new asylum, the most rational method would be to exclude all patients who had ever suffered from the disease.

As a rule, the bulk of early admissions into a new asylum are old patients who have been boarded out, or else large batches of chronic lunatics taken in under contract to help to fill the asylum, and thereby reduce the working expenses per head. In both of these cases an unduly large proportion of patients will be found whose habits are defective and who have other disagreeable attributes, for the wet and dirty lunatic is always considered to be an eminently fit and proper person to be transferred. This is just the class of case which is most prone to an attack of dysentery, and, when attacked, is almost certain to disseminate contagion lavishly amongst his neighbours. Again, a large proportion of the staff of a new asylum have had little or no experience in nursing, have not been trained to properly observe their patients, and are devoid of all knowledge of hygiene and sanitary precautions. All these things enormously favour the spread of an infective disease, and greatly increase the difficulty of coping with an epidemic of dysentery.

Indeed, the chief weapon of defence against the spread of all infec-

tive diseases is the adequate education of the staff. With an increased knowledge of their patients they become quicker at recognising when anything is wrong, and the success of all preventive measures depends to a large extent on their intelligent co-operation.

This, probably, accounts for the fact that epidemics of any magnitude are less common in the older asylums than in those newly opened.

Reference was made in the third volume of these Archives to the fact that, although dysentery was relatively as common in epilepsy as in other forms of insanity, it was comparatively rare at the Epileptic Colony, and this was attributed to the more healthy out-door life which the colonists enjoy, to the fewer number of cases aggregated together, to the vigorous methods of disinfection, and to the strict observation kept on the patient when he returns to work. No doubt the importance of isolation, disinfection, and notification of the patient on his transfer from ward to ward cannot be over-estimated; but it is as well to point out that almost all the colonists are clean, well-conducted patients, and the great majority of them enjoy good physical health. It might therefore be expected that they would be almost as immune to dysentery or phthisis as sane people living in a similar community.

When a colonist becomes permanently demented and degraded in his habits, he is obviously incapable of manual labour, and unsuitable for colony life. He is then usually transferred to one of the sister asylums, where he makes an unwelcome addition to a class of epileptics of very different type to that at the colony.

Dr. Knobel, in a contribution to "The Journal of Mental Science," in April, 1906, attempts to explain the frequency of outbreaks of dysentery in new asylums by propounding the theory that one of the normal habitats of the germ causing the disease may be the deeper layers of the soil, and shows that many epidemics of asylum dysentery have followed shortly after disturbance of the subsoil. No doubt the grounds of a new asylum are usually vigorously attacked shortly after the advent of the patients. But Dr. Knobel fails to show cause why this vindictive germ should almost invariably neglect those working patients who disturb its tranquility and attack those who toil not neither do they spin, but whose habits are defective and whose health is, as a rule, impaired.

Later on in the same paper Dr. Knobel brings evidence to show "that asylum dysentery can be caused by some micro-organism which normally inhabits the colon and becomes pathogenic when the resisting power of the tissue is sufficiently reduced."

Our cases bring but little evidence either for or against the theory that degenerative changes in the trophic nerve supply of the colon may be an important factor in the disease; but it is obvious that this can

only be a contributory factor and not the principal one, for, if the ulcers were truly trophic, no big asylum would ever be free from dysentery, nor could we account for the disease occurring in epidemic form and attacking the staff as well as the patients. Most of our patients were debilitated, some of them very feeble, and many of them were known to be the subjects of very obstinate constipation.

The disease occurred on the female side in a very virulent form; out of 20 cases there were eight deaths, and several of these occurred within three days of the onset of the attack. On the male side, out of 60 cases there were only the same number of deaths which could be directly ascribed to dysentery, but others have since died of different diseases.

Only two of our cases are recorded as having more than one attack of dysentery, but several are noted as having simple diarrhœa, either before or after the attack.

A column has been drawn in the table denoting whether the patient attacked was a direct admission from the parish or a transfer from another asylum, and, as it is a rare disease outside asylums, it is probable that but a very small percentage of the direct admissions had ever suffered previously from the disease. At the same time, it should be noted that the first case of dysentery on the female side developed in a direct admission from a workhouse infirmary after she had only been in the asylum for three days—during this time she had been kept in bed and had not mixed with other patients, and it is reasonable to suppose that she became infected before admission.

Although the disease is said to be very rare in workhouses, infirmaries, and other large institutions, there can be little doubt that it does occur; only the type of people affected in these cases do not tend to spread the disease and cause an epidemic: in other words, the conditions of these places approach more nearly to our working villas and the Epileptic Colony.

Only two cases have occurred amongst the staff, and both these were in attendants who were actually engaged in nursing the dysentery patients. Assuming the stools to be the chief source of infection, as in typhoid, these are two of the men one would have picked out as the most likely to contract the disease.

In some of our cases a mode of infection was fairly easy to guess: in other cases no source of infection could be traced, but there is always the possibility of a mild atypical case showing few or no symptoms walking about the wards and gardens and disseminating the disease.

Although there is no doubt that the stools of dysenteric patients are infectious, it is, so far as I am aware, quite unknown how long the infective organism remains in the intestines after the stools have become

normal. It may be, as Dr. Knobel suggests, that the micro-organism nominally inhabits the colon of many people, and only becomes a pathogenic under certain conditions.

Our ignorance as to how long a patient who has had dysentery remains a centre of infection, makes the question of transferring him back to the ordinary wards very difficult. It is well to isolate all those with defective habits for a long period, but it is obviously unfair to keep clean, well-conducted patients, who are capable of fully appreciating their surroundings in a ward composed chiefly of demented with defective habits. In the case of (11) H. J., for example, a boy, whose mental condition rather rapidly improved after he had recovered from an attack of dysentery, his chance of complete mental recovery would have been seriously jeopardised by prolonged association with chronic unpleasant lunatics. In those cases where the habits of the patient are cleanly, there is probably but little danger of the disease spreading. Again, some of the very excited, noisy, and turbulent patients cannot be kept for long in an infirmary ward where there are sick and dying patients whose friends are allowed to visit them at any time, and occasionally it may be necessary to transfer them back to the ordinary wards before one would care to do, if they could have been suitably accommodated in the isolation wards. In these cases, however, they can always be kept strictly apart from other patients for a further period, as urgent mental symptoms of this kind generally demand treatment in bed in a single room.

In all cases when a patient is transferred to another ward, his papers are distinctly marked, and the attendants have orders to keep careful observation on the behaviour of the bowels, and draw the attention of the doctor to anything abnormal; moreover, the patients are always accompanied by their temperature charts and clinical records, which contain an account of the disease.

The first case of dysentery at Long Grove occurred in R.1 ward on August 6th, 1907. Nine days previously a patient in the same ward, who was addicted to rubbish eating, was reported as having an attack of diarrhoea, but there was nothing in the motions or the general condition of the patient suggestive of dysentery, and, after one day in bed, he was again in his usual health. The first case (1), C. D., was a healthy man, aged 57, who was admitted into the asylum on July 12th; he had been continuously under treatment since 1903, and had been in two previous asylums; the medical superintendents of both these institutions were written to, but both reported that he had not had dysentery whilst under their care.

The attack commenced with headache and a feeling of general illness, tongue furred, breath offensive, temperature (axillary) 99·8, no

physical signs. He was transferred to J.1 ward for treatment, and the dysentery was not recognised until some 12 hours later, when he passed his first abnormal motion containing a trace of blood and a considerable quantity of mucus. He was isolated in a single room and treated with the usual precautions. The attack lasted a fortnight, but he was kept in J.1 ward for two months.

On September 6th eleven cases of diarrhœa were reported on the male side—all these cases were on mince diets, and the majority were old, feeble people—eight out of the eleven were in J.1 infirmary, nine out of the eleven were in their usual health next day, and the other two were considered as cured on the morning of the 9th and 10th respectively. The second case of dysentery (2), E. J. G., occurred in a patient suffering from general paralysis, who was admitted on August 13th direct from the parish and who had never before been under certificate. He was very demented, his habits were defective, he was generally enfeebled and had paresis of the right side. He was transferred to J.1 ward on August 28th for infirmary care. He was one of the eleven cases above mentioned that had an attack of "simple" diarrhœa lasting from September 6th to 8th; during this attack there was nothing in the motions or constitutional symptoms suggestive of dysentery, and on the morning of September 9th he was considered to be in his usual somewhat feeble health. On the same evening his temperature rose to 103° and he passed a motion containing almost pure blood with some mucus. His attack of dysentery lasted about a week. It is possible either that his preliminary diarrhœa was really dysentery, or that it had lowered the power of resistance of the bowel to bacterial infection. Either of these suppositions, if true, may account for the fact which has been noted by some observers that epidemics of dysentery often coincide with an increase in the number of cases of simple diarrhœa. It will be seen that (1), C. D., the only known source of the disease up to this time was still in J.1 ward. The next three cases occurred in R.1 ward, two being "transfer" patients and one a "direct" admission. The history of one of the transfer patients (5), T. W., recorded an attack of simple diarrhœa in July, the same year, but in neither of the others was there any history of bowel trouble.

It will be seen from the table that after dysentery had once started, the male side was never free from the disease for more than a few weeks, but in May, June, and July, 1908, only three cases occurred in the whole asylum.

Several other cases are worthy of special mention: Case (7), H. C., a quiet, clean, well-conducted imbecile, was transferred from O.2 ward to J.1 ward on November 2nd, as he needed rest in bed for synovitis of the knee due to injury. He was nursed in the same dormitory as the



dysentery patients, and on November 5th he developed the disease. There is a strong probability that he became infected in J.1 ward, as there has been no case before or since in O.2 ward, and from the history of the patient it appears that he had been free from any attack of a diarrhœcal or dysenteric nature during his  $4\frac{1}{2}$  years' residence at the previous asylum. This suggests that the incubation period may be four days or less.

Case (11) is rather puzzling: H. J., a boy of 18, suffering from acute mania, first attack, was admitted direct from the infirmary on December 17th to N.1 ward. On December 24th he developed dysentery. Up to that time he had mixed very little with other patients in the ward, as he was in bed in the padded room on account of mental excitement. His habits were wet and dirty. There had been no previous cases from this ward, nor had any been returned there. The attack commenced suddenly with malaise and abdominal pains; there were numerous motions containing blood and mucus, but there was no pyrexia, and the mental symptoms abated. He was given a large dose of castor oil, and was apparently well in two days, the motions after this being normal and the mental symptoms returning. There is no doubt that he had a short or abortive attack of asylum dysentery.

Case (16), F. W. G., a patient suffering from general paralysis, was transferred to J.1 on January 1st, 1908; convulsive seizures and transient paralysis occurred. The patient became progressively weaker, and died on March 18th. He was wet and dirty—passed everything in the bed—the motions were certainly carefully observed and were reported as being normal; no blood or mucus was ever seen. At the autopsy very extensive ulceration of the colon was discovered. One other case, (45), W. W., passed normal motions, which were seen by the doctor, for two days preceding death, and *post mortem* there was very extensive ulceration of the whole of the large intestine. One male patient had two attacks, W. W., (13) and (19). The first attack lasted eight weeks, and a similar interval separated the two attacks. One female, Case M. S., had three attacks in nine months, (4), (11), (19), in the third of which she died, and another female, Case J. A. F., (13), was discovered to have ulceration of the colon, which appeared to be of very long standing, though she died within a few hours of the commencement of her acute attack. If some of these case of second attacks are really cases of chronic or relapsing dysentery, in which, in spite of the absence of all symptoms, the ulceration has never entirely healed and which still remains infective and subject of acute exacerbations of the disease, they are a very real danger to the community with whom they are housed, more especially when their habits are defective; and at present there appears to be no way of diagnosing these cases until they have had more than one attack

or exacerbation. Another possible way of the disease spreading is that some patients who have suffered from it may act as "dysentery carriers," that is to say, although they completely recover, the germ remains in some part of their intestinal tracts for months or years. Some epidemics of typhoid have been proved to originate in this manner from the so-called "typhoid carrier," who though apparently quite healthy themselves pass typhoid bacilli in the stools.

The two female cases just referred to are worth recording in a little more detail. The first, M. S., (4), (11), (19), was a transfer who had been under certificate since 1898, and had been in two previous asylums. She had an attack at Claybury lasting from November 19th to December 1st, 1899; she relapsed on December 15th and recovered on January 14th, 1900. She had a second attack in 1902; she was transferred to another asylum in 1903, and during her four years there is said to have been free from dysentery and diarrhœa. Her first attack at Long Grove commenced on January 15th, 1908, and she was regarded as cured on 8th of February. Her next attack lasted from July 5th to 18th. On September 22nd she was noticed to be looking ill, and the temperature was found to be  $105^{\circ}$ ; the next day she was quite collapsed with signs of symptoms of peritonitis; she died the same evening. She had vomited once, but there had been no action of the bowel since the commencement of her acute illness. *Post mortem* there were old peritoneal adhesions around the lower part of the colon in the left lower quadrant of the abdomen; there was recent peritonitis and some semi-purulent fluid in the lower part of the abdomen and pelvis; no actual perforation was found, but there were many peritoneal adhesions which made the examination for this very uncertain. The whole of the mucous membrane of the middle portion of the sigmoid colon was gangrenous. There were no signs of old ulceration and no thickening of the coats of the bowel. This is the only one of our autopsies in which there were peritoneal complications.

The second case, J. A. F., (13), was admitted to the Female Hospital Villa on July 2nd, 1908, suffering from melancholia of the agitated form. She did not improve in any way, her mental symptoms became more marked, she was intensely restless and apprehensive, very defective in her habits, at times refused food, and had to be fed by nasal tube. On August 28th, at 2.15 a.m., she had a rigor after which she collapsed. The bowels were relaxed twice. She was treated with stimulants, etc., but never rallied, and she died at 4.20 a.m. The motions did not contain blood or mucus, and the dysentery was not recognised during life. At the autopsy she was found to have pneumonia and very extensive ulceration of the colon. The ulcers were round and oval with thickened bases and edges and around them was much pigmentation; they had the

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appearance of being of long standing. There was also much general congestion of the colon and very extensive superficial loss of mucous membrane, so she probably had an acute attack of dysentery supervening upon an old chronic dysenteric ulceration. This patient was a direct admission to the asylum, and had never been previously certified. She had once before been under treatment at an infirmary for mental disorder. There had only been one case of dysentery previously at the Hospital Villa, and this had occurred four months before, and no cases that had suffered from dysentery had been transferred back to this villa.

The first of the following tables has already been referred to. The second gives a short abstract of the *post-mortem* notes on the condition of the bowel in those cases which died either directly from dysentery or from some other disease after recovering from dysentery.

The third table is a record of the ward-to-ward transfers of all the cases both before and after the attack. It will be noticed that many of the cases have been in numerous different wards; this is unavoidable in the opening of a new asylum, and the moves are likely to be much fewer now that the institution is full. In the last table an asterisk indicates the ward at the time of onset of the dysentery.

TABLE I.—MALES.

Name.	Age.	No.	Admission.	Transfer.	Mental State.	Habits.	Employ.	Wards.	Health.	Onset.	Recovery.	Death.	Remarks.
1. C. D.	57	248	12-7-07	1	Delusional ... G. P. I.	Clean ...	Ward	R. 1	Good ...	6-8-07	10-9-07	—	Reported as having dietetic diarrhoea from 6-9-07 to 8-9-07.
2. E. J. G.	31	335	13-8-07	1	—	Defective ...	Nil.	J. 1	Impaired ...	9-9-07	15-9-07	—	—
3. E. M.	57	361	17-8-07	1	Dementia ... G. P. I.	W. & D. ...	Nil.	R. 1	Impaired ...	29-9-07	24-10-07	—	Had attack of simple diarrhoea, July, 1907. (Mitral stenosis.)
4. F. S.	31	303	2-8-07	1	—	Clean ...	Farm	R. 1	Moderate ...	7-10-07	24-10-07	—	—
5. T. W.	63	561	23-9-07	1	Melancholia	Clean ...	Ward	R. 1	Fair ...	23-10-07	11-11-07	—	—
6. H. C.	75	234	12-7-07	1	Dementia ...	Careless ...	Gardens	H. 1	Poor ...	24-10-07	11-11-07	—	—
7. H. C.	41	4	18-6-07	1	Imbecility	Clean ...	Ward	J. 1	Good ...	5-11-07	22-11-07	—	—
8. J. M.	36	226	12-7-07	1	Delusional ...	Careless ...	Ward	R. 1	Fair ...	21-11-07	4-12-07	—	—
9. J. D.	62	422	11-9-07	1	G. P. I.	Depraved ...	Nil.	K. 1	Feeble ...	22-11-07	7-12-07	13-2-08	P. M.
10. W. H. A.	36	461	13-9-07	1	G. P. I.	Defective ...	Nil.	K. 1	Feeble ...	22-11-07	4-12-07	10-1-08	P. M.
11. H. J.	18	838	17-12-07	1	Acute Mania	W. & D. ...	Nil.	N. 1	Good ...	24-12-07	26-12-07	—	Patient since discharged. Recovered.
12. G. W.	63	562	23-9-07	1	Gross Brain Lesion	Careless ...	Nil.	H. 1	Impaired ...	28-12-07	13-1-08	—	Hemiplegia.
13. W. W.	36	419	30-8-07	1	Dementia ... G. P. I.	W. & D. ...	Nil.	N. 1	Poor ...	1-1-08	24-2-08	—	Had subsequent attack 16-4-08.
14. G. E. C.	39	338	14-8-07	1	—	W. & D. ...	Nil.	J. 1...	Impaired ...	26-2-08	—	7-9-08	Had attack of diarrhoea 22-8-07 lasting 24 hours. P. M.
15. H. H. T.	32	599	23-9-07	1	Dementia c Ep.	W. & D. ...	Nil.	O. 1	Fair ...	4-3-08	4-4-08	—	Not diagnosed before death. P. M.
16. F. W. G.	48	413	20-8-07	1	G. P. I.	W. & D. ...	Nil.	J. 1...	Feeble ...	25-3-08	11-4-08	—	Probably tuberculous enteritis.
17. T. M.	68	266	13-7-07	1	Gross Brain Lesion	Depraved ...	Nil.	J. 1...	Feeble ...	31-3-08	30-4-08	—	P. M.
18. A. J.	19	773	11-11-07	1	G. P. I.	W. & D. ...	Nil.	J. 1...	Feeble ...	—	—	—	See No. 13. Previous attack.
19. W. W.	36	419	30-8-07	1	Dementia ...	W. & D. ...	Nil.	K. 1	Poor ...	16-4-08	15-5-08	—	—
20. R. R.	76	162	5-7-07	1	Dementia ...	Defective ...	Nil.	H. 1	Poor ...	20-4-08	12-5-08	—	—
21. C. M.	31	734	16-10-07	1	Dementia c Ep.	W. & D. ...	Nil.	M. 1	Fair ...	20-4-08	4-5-08	—	—
22. H. W.	66	228	12-7-07	1	Dementia ...	Defective ...	Nil.	H. 1	Feeble ...	20-4-08	80-5-08	—	—
23. S. C.	72	123	28-6-07	1	Dementia ...	Defective ...	Nil.	H. 1	Feeble ...	21-4-08	30-4-08	—	—
24. E. H.	33	—	—	Staff	—	—	—	J. 1...	Good ...	23-4-08	7-5-08	—	Was nursing the dysentery patients, and sleeping in J. 1 ward, when he contracted disease.
25. W. A.	55	836	16-12-07	1	Dementia ...	Clean ...	Nil.	H. 1	Bad ...	7-5-08	30-5-08	—	Morbus cordis.
26. P. C. F.	53	519	23-9-07	1	Dementia ...	W. & D. ...	Nil.	O. 1	Fair ...	23-6-08	10-7-08	—	Sanatorium, opened as Dysentery Villa.
27. J. R. S.	71	765	30-10-07	1	Dementia ...	W. & D. ...	Nil.	J. 1...	Feeble ...	23-8-08	—	8-9-08	P. M.
28. R. G.	63	699	14-10-07	1	Dementia c Ep.	Defective ...	Nil.	H. 1	Feeble ...	23-8-08	6-9-08	—	Tertiary syphilis.
29. E. J. V.	42	1116	20-5-08	1	Delusional ...	Clean ...	Nil.	N. 1	Impaired ...	30-8-08	6-9-08	—	Chronic constipation.
30. H. W. H.	36	521	23-9-07	1	Delusional ...	Degraded ...	Nil.	N. 1	Poor ...	30-8-08	8-9-08	—	—

TABLE 1.—MALES.—continued.

Name.	No.	Admission.	Transfer.	Mental Stage.	Habits.	Employ.	Wards.	Health.	Onset.	Recovery.	Death.	Remarks.
31. F. B.	28	27-5-08	1	Melancholia	Degraded	Nil.	N. 1	Impaired	30-8-08	6-9-08	—	Tertiary syphilis.
32. F. R.	38	17-11-07	1	Melancholia	Clean	Nil.	M. 1	Fair	31-8-08	23-9-08	—	Chronic constipation.
33. J. B.	66	21-6-07	1	Delusional	Careless	Nil.	N. 1	Fair	1-9-08	6-9-08	—	
34. W. F.	34	10-8-07	1	G. P. I.	Defect	Nil.	N. 1	Impaired	1-9-08	6-9-08	15-9-08	P. M.
35. E. F. B.	63	1-10-07	1	Dementia	W. & D.	Nil.	K. 1	Feeble	4-9-08	9-9-08	—	Urine orinker.
36. J. C. T.	38	3-2-08	1	G. P. I.	W. & D.	Nil.	K. 1	Impaired	4-9-08	6-9-08	—	
37. M. M.	40	16-10-07	1	Dementia	Depraved	Nil.	K. 1	Poor	4-9-08	14-9-08	—	
38. C. W. P.	38	3-3-08	1	G. P. I.	Depraved	Ward	K. 1	Poor	4-9-08	6-9-08	—	
39. F. P.	21	17-2-08	1	Dementia	W. & D.	Nil.	K. 1	Fair	3-9-08	6-9-08	—	
40. J. B.	42	25-5-07	1	G. P. I.	Degraded	Nil.	N. 1	Impaired	1-9-08	8-9-08	—	
41. A. J.	41	8-12-07	1	Dementia c Ep.	W. & D.	Nil.	J. 1...	Impaired	3-9-08	20-9-08	—	
42. W. B. B.	20	12-7-07	1	Dementia c Ep.	W. & D.	Nil.	O. 1	Feeble	5-9-08	13-9-08	—	
43. T. W.	42	12-2-08	1	Dementia c Ep.	Careless	Nil.	R. 1	Fair	7-9-08	14-9-08	—	
44. C. L.	54	30-5-08	1	G. P. I.	W. & D.	Nil.	J. 1...	Impaired	11-9-08	20-9-08	—	Motions normal for 2 days before death. P. M.
45. W. W.	32	12-5-08	1	G. P. I.	W. & D.	Nil.	N. 1	Impaired	12-9-08	—	13-10-08	Night Attendant in Sanatorium Dycentery Dormitory. Was frequently tube fed.
46. J. F.	33	1-10-07	Staff	—	—	—	Sanatorium	Good	9-9-08	12-9-08	—	
47. M. H.	41	17-9-07	1	Delusional	W. & D.	Nil.	N. 1	Fair	9-9-08	13-9-08	—	
48. J. H. H.	28	27-5-08	1	G. P. I.	W. & D.	Nil.	J. 1...	Feeble	18-9-08	21-9-08	—	
49. C. R. G.	35	27-8-07	1	G. P. I.	Clean	Nil.	N. 1	Impaired	14-9-08	21-9-08	—	
50. S. F. G.	54	16-6-08	1	G. P. I.	Depraved	Nil.	N. 1	Impaired	14-9-08	20-9-08	—	
51. J. B.	60	2-8-07	1	G. P. I.	W. & D.	Nil.	K. 1	Feeble	13-9-08	20-9-08	—	
52. S. G. E.	64	13-8-08	1	Dementia	W. & D.	Nil.	J. 1...	Feeble	22-9-08	—	5-10-08	P. M. objected to.
53. J. T. J. R.	53	12-7-07	1	Dementia	Careless	Nil.	O. 1	Fair	25-9-08	20-10-08	—	
54. F. C.	42	11-5-08	1	G. P. I.	W. & D.	Nil.	Sanatorium	Feeble	5-10-08	19-10-08	—	
55. H. T.	67	23-9-07	1	Dementia	W. & D.	Nil.	Sanatorium	Feeble	6-10-08	21-10-08	—	
56. W. M.	49	3-7-08	1	Mania	W. & D.	Nil.	J. 1...	Feeble	15-10-08	—	22-10-08	Phthisis. P. M.
57. W. B.	22	23-9-07	1	Dementia	W. & D.	Nil.	O. 1	Fair	30-10-08	3-11-08	—	Had attack of diarrhoea dietetic lasting from 7-9-08 to 9-9-08.
58. J. J. S.	52	16-9-07	1	Delusional	Clean	Farm	F. V.	Fair	27-10-08	3-11-08	—	
59. J. E.	52	12-7-07	1	Volitional	Careless	Nil.	N. 1	Fair	28-10-08	2-11-08	—	
60. J. C. H.	39	27-6-08	1	G. P. I.	Degraded	Nil.	Sanatorium	Feeble	30-10-08	—	3-11-08	P. M.

The following shows the number of cases of Dysentery in each ward. The figures in brackets being the ward accommodation:—  
H. 2 (32), 0; J. 2 (51), 0; K. 2 (44), 0; M. 2 (45), 0; N. 2 (52), 0; O. 2 (60), 0; R. 2 (60), 0;  
H. 1 (34), 7; J. 1 (50), 13; K. 1 (44), 9; M. 1 (45), 2; N. 1 (49), 18; O. 1 (60), 5; R. 1 (60), 6; S. (120), 0;  
Sanatorium (60), 4; Farmstead (60), 1; South View (65), 0; Prospect Villa (25), 0; Hospital (50), 0.

TABLE II.—FEMALES.

Name.	Age.	No.	Admission.	Transfers.	Mental State.	Habits.	Employ.	Wards.	Health.	Onset.	Recovery.	Death.	Remarks.
1. A. B.	68	424	20-9-07	1	Insanity c Ep.	Clean	Nil	C. 1	Moderate	23-9-07	4-11-07	—	Developed 3 days after admission
2. M. G.	57	181	11-7-07	1	Dementia	W. & D.	Nil	F. 1	Feeble	12-10-07	4-11-07	—	Had two subsequent attacks.
3. K. R.	34	63	21-6-07	—	Imbecility	Clean	Nil	B. 1	Good	21-10-07	4-11-07	—	History of attack some years before P. M.
4. M. S.	45	131	10-7-07	1	Dementia	W. & D.	Nil	D. 1	Poor	15-1-08	8-2-08	23-9-08	No symptoms of dysentery for a fortnight before death. P. M.
5. E. D.	75	280	8-8-07	1	Dementia	Filthy	Nil	D. 1	Bad	22-1-08	8-2-08	19-2-08	Had to be tube fed. P. M.
6. M. A. B.	56	689	4-11-07	1	Melancholia	Faulty	Nil	C. 1	Poor	19-1-08	—	21-1-08	Very thin. P. M.
7. C. H.	45	732	20-11-07	1	Mania Chronic	Degraded	Nil	F. 1	Poor	23-1-08	—	26-1-08	Subsequently had diarrhoea, lasting from 10-5-08 to 12-5-08.
8. B. S.	30	541	7-10-07	—	Mania Chronic	Clean	Nil	D. 1	Fair	14-3-08	27-3-08	—	P. M.
9. E. A. C.	23	691	4-11-07	1	Mania Chronic	Faulty	Nil	Hospital	Fair	29-3-08	11-4-08	—	Had previous attack (No. 4).
10. E. M. A.	51	383	12-9-07	1	Mania	W. & D.	Nil	C. 2	Fair	22-4-08	—	28-4-08	Previously had diarrhoea from 10-5-08 to 12-5-08.
11. M. S.	46	131	10-7-07	1	Dementia	W. & D.	Nil	F. 1	Poor	6-7-08	18-7-08	—	Had to be tube fed. Morbus cordis. P. M.
12. M. D.	63	607	23-10-07	—	Dementia	W. & D.	Nil	F. 1	Poor	14-8-08	17-8-08	—	Spinal disease.
13. J. A. F.	66	1072	2-7-08	1	Melancholia	Faulty	Nil	Hospital	Impaired	27-8-08	—	28-8-08	Had diarrhoea from 10-5-08 to 12-5-08.
14. E. G.	20	823	10-2-08	1	Dementia	Faulty	Nil	F. 1	Impaired	28-8-08	12-9-08	—	P. M.
15. M. B.	77	268	30-7-07	1	Dementia	W. & D.	Nil	F. 1	Feeble	28-8-08	—	31-8-08	P. M.
16. J. H.	48	632	28-10-07	1	Dementia	W. & D.	Nil	D. 1	Poor	1-9-08	—	2-9-08	Previous attacks Nos. 4 & 11. P. M.
17. J. M.	45	1086	3-7-08	1	Delusional	W. & D.	Nil	F. 1	Feeble	2-9-08	—	19-9-08	
18. E. C.	24	915	11-4-08	1	Mania	Clean	Ward	C. 1	Good	2-9-08	9-9-08	—	
19. M. S.	46	131	10-7-07	1	Dementia	W. & D.	Nil	D. 1	Poor	22-9-08	—	23-9-08	
20. S. G.	40	259	30-7-07	1	Dementia	W. & D.	Nil	F. 1	Feeble	22-10-08	31-10-08	—	

The following shows the number of cases of Dysentery in each ward. The figures in brackets being the ward accommodation :—

A 2 (65), 0; B 2 (65), 0; C 2 (50), 1; D 2 (46), 0; E 2 (46), 0; F 2 (65), 0; G 2 (83), 0;  
 A 1 (64), 0; B 1 (64), 1; C 1 (50), 8; D 1 (46), 5; E 1 (44), 0; F 1 (51), 8; G 1 (38), 0; L (120), 0;  
 Hospital (63), 2; Grove Villa (67), 0; Homestead (32), 0.

## TABLE III.—MALES.

## SHORT ABSTRACT OF P. M. REPORT ON CONDITION OF INTESTINES.

9. J. D., 452.—Intestines appeared normal, no ulceration, no scars. Cause of death, general paralysis.

10. W. H. A., 461.—No signs of old or recent ulceration. Cause of death, general paralysis.

14. G. E. C., 338.—Superficial ulceration of the whole of the large intestines, only small islands of normal mucous membrane left.

16. F. W. G., 413.—Extensive recent ulceration throughout the whole of the large intestine; the ulcers were still discrete and varied from the size of a pea to that of a shilling.

18. A. J., 773.—Tuberculous ulcers of both large and small intestine.

27. J. R. S., 765.—Typical dysenteric ulceration of rectum and sigmoid; the edges of the ulcers were not thickened and the ulceration appeared to be quite recent.

35. E. F. B., 630.—Very extensive recent ulceration of whole of large intestine, most marked in sigmoid and rectum. No signs of old ulceration.

45. W. W., 1105.—Very extensive ulceration of the whole of the large intestine.

56. W. M., 1238.—Mucous membrane of large intestine much congested throughout, with some superficial loss of surface. Four typical dysenteric ulcers in cæcum.

60. J. C. H., 1223.—Lower part of colon greatly congested, numerous superficial erosions of mucous membrane.

In three of these cases—9, 10, and 18—dysentery could not be said to directly contribute to death. In one case, No. 52, no autopsy was done on account of objection by friends.

This gives a case mortality of 13·3 per cent. for the males.

## TABLE IV.—FEMALES.

## SHORT ABSTRACT OF P. M. REPORT ON CONDITION OF INTESTINES.

5. E. D., 280.—Numerous slaty grey patches on mucous membrane of colon, no congestion, no ulceration.

6. M. A. B., 689.—Mucous membrane much congested with patches of a slaty grey colour. One ulcer in cæcum, and areas of superficial necrosis.

7. C. H., 732.—Acute necrosis of mucous membrane of large intestine, with superficial ulceration.

10. E. M. A., 383.—In upper part of large intestine were small areas of ulceration and intense congestion. In the lower part the whole of the mucous membrane was sloughing.

13. J. A. F., 1072.—Marked congestion throughout the large intestine. Numerous ulcers, round and oval, in colon; edges thickened and pigmented, and some show thickening at base, they have every appearance of being old; there is also very extensive superficial loss of mucous membrane which appears to be recent.

15. M. B., 268.—Intense congestion of mucosa of large intestine with extensive superficial ulceration, giving it a worm-eaten appearance.

16. J. H., 632.—Whole mucosa intensely congested with irregular superficial ulcers scattered throughout.

17. J. M., 1086.—Intense congestion of both small and large intestine, small ulcers in the last six inches of the ileum and very extensive ulceration throughout the whole of the colon.

19. M. S., 131.—Old peritoneal adhesions and recent peritonitis; the whole of the mucous membrane of the middle portion sigmoid was sloughing.

In the first of these cases there were no symptoms of dysentery for a fortnight before death and the patient died from other causes. This leaves eight deaths out of 20 cases, giving a case mortality of 40 per cent., or three times as great as the case mortality on the male side.

TABLE V.—TRANSFERS OF MALE PATIENTS FROM WARD TO WARD.

Name.	No.	Admitted to Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.	Ward.	Date.
1. C. D.	248	12-7-07	*R. 1	6-8-07	J. 1	4-10-07	J. 2	11-10-08	R. 2	11-10-08	R. 2	10-12-07	R. 2	13-11-08	S. V.			
2. E. G.	835	13-8-07	*R. 1	20-8-07	M. 1	28-8-07	*J. 1	21-4-08	H. 1	21-4-08	H. 1	28-11-07	H. 2	2-3-08	S. V.			
3. E. M.	361	17-8-07	*R. 1	29-9-07	J. 1	21-11-07	R. 1	18-11-07	J. 2	18-11-07	J. 2	28-11-07	H. 1	2-3-08	S. V.			
4. D. G. S.	303	2-8-07	N. 1	28-8-07	*R. 1	7-10-07	J. 1	23-10-07	J. 1	23-10-07	J. 1	24-10-07	H. 1	2-3-08	S. V.			
5. T. W.	561	23-9-07	M. 2	1-10-07	*R. 1	21-9-07	*H. 1	23-10-07	J. 1	23-10-07	J. 1	24-10-07	H. 1	2-3-08	S. V.			
6. P. C.	234	12-7-07	R. 1	24-8-07	F. V.	3-12-07	J. 2	27-12-07	S. V.	27-12-07	S. V.	4-1-08	H. 2	2-3-08	S. V.			
7. H. C.	4	18-6-07	O. 2	2-11-07	*J. 1	18-12-07	K. 2	3-10-08	S. V.	3-10-08	S. V.	18-11-07	*K. 1	22-11-07	J. 1			
8. J. M.	226	12-7-07	*R. 1	21-11-07	J. 1	15-10-07	H. 1	22-10-07	J. 1	22-10-07	J. 1	23-9-07	J. 1	22-11-07	J. 1			
9. J. D.	452	11-9-07	N. 1	23-9-07	J. 1	15-10-07	H. 1	22-10-07	J. 1	22-10-07	J. 1	23-9-07	J. 1	22-11-07	J. 1			
10. W. A.	461	13-9-07	*R. 1	6-11-07	*K. 1	20-11-07	J. 1	29-2-08	R. 2	29-2-08	R. 2	29-2-08	R. 2	22-11-07	J. 1			
11. H. J.	838	17-12-07	*N. 1	25-12-07	J. 1	16-2-08	N. 1	16-2-08	H. 1	16-2-08	H. 1	16-2-08	H. 1	22-11-07	J. 1			
12. G. W.	562	23-9-07	M. 2	15-10-07	*H. 1	30-12-07	J. 1	16-4-08	J. 1	16-4-08	J. 1	16-4-08	J. 1	22-11-07	J. 1			
13. W. W.	419	30-8-07	*N. 1	1-1-08	J. 1	4-3-08	K. 1	26-2-08	*J. 1	26-2-08	*J. 1	26-2-08	*J. 1	22-11-07	J. 1			
14. G. E. C.	338	14-8-07	N. 1	15-11-07	J. 1	31-1-08	K. 1	13-10-08	O. 1	13-10-08	O. 1	26-2-08	*J. 1	22-11-07	J. 1			
15. H. T.	519	23-9-07	M. 2	25-9-07	*O. 1	4-9-08	J. 1	21-1-08	*J. 1	21-1-08	*J. 1	21-1-08	*J. 1	22-11-07	J. 1			
16. F. G.	413	28-8-07	N. 1	7-9-07	R. 1	22-11-07	H. 1	21-1-08	*J. 1	21-1-08	*J. 1	21-1-08	*J. 1	22-11-07	J. 1			
17. T. M.	266	13-7-07	N. 1	1-8-07	*J. 1	14-1-08	K. 1	25-3-08	*J. 1	25-3-08	*J. 1	25-3-08	*J. 1	22-11-07	J. 1			
18. A. J.	773	11-11-07	N. 1	16-11-07	J. 1	4-3-08	*K. 1	16-4-08	J. 1	16-4-08	J. 1	16-4-08	J. 1	22-11-07	J. 1			
19. W. W.	419	30-8-07	N. 1	1-1-08	J. 1	4-3-08	*K. 1	16-4-08	J. 1	16-4-08	J. 1	16-4-08	J. 1	22-11-07	J. 1			
20. R. R.	162	5-7-07	O. 1	9-8-07	*H. 1	20-4-08	J. 1	9-5-08	M. 1	9-5-08	M. 1	9-5-08	M. 1	22-11-07	J. 1			
21. C. M.	734	16-10-07	K. 2	16-10-07	*M. 1	19-4-08	J. 1	9-5-08	M. 1	9-5-08	M. 1	9-5-08	M. 1	22-11-07	J. 1			
22. H. W.	228	12-7-07	R. 1	15-10-07	H. 1	1-4-08	*H. 1	20-4-08	J. 1	20-4-08	J. 1	20-4-08	J. 1	22-11-07	J. 1			
23. S. C.	123	28-6-07	M. 1	15-10-07	*H. 1	21-4-08	J. 1	1-5-08	H. 1	1-5-08	H. 1	1-5-08	H. 1	22-11-07	J. 1			
24. E. H.	836	16-12-07	N. 1	18-12-07	*H. 1	7-5-08	J. 1	11-6-08	*H. 1	11-6-08	*H. 1	11-6-08	*H. 1	22-11-07	J. 1			
25. F. A.	519	23-9-07	N. 1	24-9-07	*O. 1	29-6-08	Sana.	7-9-08	O. 1	7-9-08	O. 1	7-9-08	O. 1	22-11-07	J. 1			
26. P. F.	745	29-10-07	R. 1	31-10-07	H. 1	10-3-08	O. 1	19-5-08	*J. 1	19-5-08	*J. 1	19-5-08	*J. 1	22-11-07	J. 1			
27. R. J. S.	699	14-10-07	K. 1	27-10-07	O. 1	3-12-07	*H. 1	29-8-08	Sana.	29-8-08	Sana.	29-8-08	Sana.	22-11-07	J. 1			
28. R. G.	1816	20-5-08	H. V.	6-7-08	*N. 1	30-8-18	Sana.	5-10-08	N. 1	5-10-08	N. 1	5-10-08	N. 1	22-11-07	J. 1			
29. J. V.	1816	20-5-08	H. V.	6-7-08	*N. 1	30-8-18	Sana.	5-10-08	N. 1	5-10-08	N. 1	5-10-08	N. 1	22-11-07	J. 1			
30. H. H.	1221	23-9-07	*N. 1	11-8-08	Sana.	13-10-08	O. 1	31-8-08	Sana.	31-8-08	Sana.	31-8-08	Sana.	22-11-07	J. 1			
31. F. B.	1138	27-5-08	H. V.	15-6-08	O. 1	24-6-08	*N. 1	31-8-08	Sana.	31-8-08	Sana.	31-8-08	Sana.	22-11-07	J. 1			
32. F. R.	780	16-11-07	N. 1	17-2-08	H. V.	2-5-08	*M. 1	31-8-08	Sana.	31-8-08	Sana.	31-8-08	Sana.	22-11-07	J. 1			
33. J. B.	53	21-6-07	N. 1	13-7-07	R. 1	16-8-07	R. 2	3-9-07	O. 2	3-9-07	O. 2	3-9-07	O. 2	22-11-07	J. 1			
34. W. F.	329	10-8-07	N. 1	21-2-08	R. 1	12-6-08	R. 2	20-8-08	*N. 1	20-8-08	*N. 1	20-8-08	*N. 1	22-11-07	J. 1			
35. F. B.	630	1-10-07	K. 2	28-3-08	K. 1	22-4-08	J. 1	24-7-08	*K. 1	24-7-08	*K. 1	24-7-08	*K. 1	22-11-07	J. 1			
36. J. T.	915	3-2-08	N. 1	12-2-08	N. 1	18-2-08	N. 1	26-5-08	*K. 1	26-5-08	*K. 1	26-5-08	*K. 1	22-11-07	J. 1			
37. M. M.	741	16-10-07	K. 2	10-11-07	H. 1	27-11-07	J. 1	8-2-08	N. 2	8-2-08	N. 2	8-2-08	N. 2	22-11-07	J. 1			
38. C. S.	1025	30-3-08	H. V.	6-4-08	N. 1	21-7-08	*K. 1	4-9-08	Sana.	4-9-08	Sana.	4-9-08	Sana.	22-11-07	J. 1			
39. F. P.	968	17-2-08	N. 1	24-3-08	*K. 1	5-9-08	Sana.	1-9-08	Sana.	1-9-08	Sana.	1-9-08	Sana.	22-11-07	J. 1			
40. J. B.	1173	15-6-18	H. V.	23-6-08	J. 1	24-6-08	*N. 1	18-10-08	J. 1	18-10-08	J. 1	18-10-08	J. 1	22-11-07	J. 1			
41. A. J.	880	6-12-07	N. 1	24-6-08	*J. 1	3-9-08	Sana.	9-3-08	*O. 1	9-3-08	*O. 1	9-3-08	*O. 1	22-11-07	J. 1			
42. W. B. B.	223	12-7-07	R. 1	12-8-07	O. 1	31-1-08	J. 1	9-3-08	*O. 1	9-3-08	*O. 1	9-3-08	*O. 1	22-11-07	J. 1			





## CONCLUSIONS.

From studying the literature and from clinical experience, I have come to the following conclusions:—

(1) That "Asylum Dysentery" is an infectious disease caused by the action of an organism or group of organisms.

(2) That the disease is communicable mainly if not solely by contact with the excreta of infected persons.

(3) That the disease is by no means confined to asylums or to the insane, but that the frequency of its occurrence in epidemic form in asylums is largely accounted for by the defective habits of many of the inmates.

(4) That the disease occurs in patients suffering from all forms of mental disorders but chiefly those in feeble physical health, and that the great majority of patients attacked are of defective habits.

(5) That there is no evidence supporting the suggestion that a nervous or trophic condition has any direct influence in the causation of the disease, but that the persons attacked are frequently those subject to severe and chronic constipation, which may be regarded as a predisposing cause.

(6) That different epidemics of the disease vary greatly in virulence.

(7) That the disease occurs in many mild atypical and abortive forms which are difficult to recognise, and that in spite of all reasonable care it is frequently diagnosed as "simple" diarrhoea or escapes recognition altogether.

(8) It is highly probable that some persons who have had the disease become "dysentery carriers," and that the organism causing the disease continues to live in the intestine, possibly causing recurrent attacks of dysentery or possibly causing no symptoms in the "carrier" but capable of transmitting the disease to others.

(9) The isolation of all suspicious cases and disinfection of all clothing with which the patient has been in contact are essential.

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STATISTICS RELATING TO THE PERCENTAGE INCIDENCE  
OF INTRACEREBRAL AND SUBDURAL HÆMORRHAGE  
AND DEPOSIT IN THE INSANE.

By F. W. MOTT, M.D., F.R.S., F.R.C.P.

I have collected the statistics relating to 1,926 necropsies conducted at Claybury Asylum by my assistants or myself during the past ten years, with a view of ascertaining the percentage incidence of intracerebral and subdural hæmorrhage and deposit in the insane. The results are recorded in the subjoined table, from which the following conclusions may be deduced. The total percentage of intracerebral hæmorrhage is 1·2 per cent. With the exception of two cases of doubtful general paralysis, the hæmorrhage occurred in the subjects of insanity other than general paralysis. In the case of subdural hæmorrhage and deposit, especially in males, there appeared to be two separate morbid conditions: (a) Cases of undoubted subdural hæmorrhage in elderly people associated with arterial degeneration and cardiac hypertrophy; (b) Cases of membrane formation of a similar nature to that found in general paralysis. Among the females the former class of case was not in evidence. Combining therefore the intracerebral and subdural types of hæmorrhage we have a sum total of 35 cases out of 1,926 necropsies, which is about 2 per cent. In practically every case of intracerebral and subdural hæmorrhage there was associated chronic vascular and renal disease (*vide* Table); a condition markedly different from that found in cases of chronic pachymeningitis, in which the heart, together with the other viscera, usually showed some wasting; especially was this the case in the subjects of general paralysis of the insane.

	Male.	Female.
Average weight of the insane heart in grams* ... ..	300	270
Average weight of the heart in the cases of intracerebral hæmorrhage (M. 16; F. 9) ... ..	400	306
Weight of heaviest heart ... ..	600	440
Weight of lightest heart ... ..	310	200
Number of hearts above average weight ... ..	16	5
Number of hearts below average weight ... ..	...	4

\* Obtained from an average of 100 male and 100 female consecutive autopsies.

	Male.	Female.
Average weight of heart in cases of subdural hæmorrhage other than general paralysis of the insane (M. 12; F. 1) ...	402	205†
Number of hearts above the average weight ...	10	...
Weight of heaviest heart ...	540	...
Weight of lightest heart ...	290	...
Average weight of heart in cases of hæmorrhagic pachymeningitis other than general paralysis (M. 7; F. 13) ...	275	238
Average weight of heart in cases of hæmorrhagic pachymeningitis of general paralysis (M. 18; F. 2) ...	290	257
Total number of deaths (out of 1,926) occurring at 45 years and under ...	355	343
Number of cases of intracerebral hæmorrhage occurring at 45 years or under ...	3	1
Number of cases of subdural hæmorrhage and pachymeningitis other than general paralysis occurring at 45 years or under ...	1	1
Number of cases of hæmorrhagic pachymeningitis in general paralysis occurring at 45 years or under ...	11	1

† One case only.

TABLE showing the incidence of Cerebral Hæmorrhage and Chronic Pachymeningitis in the Insane.

	Males.	Females.	Total.
Total number of necropsies performed ...	937	989	1926
Number of cases of general paralysis ...	334	127	461
" insanity other than general paralysis ...	603	862	1465
" intracerebral hæmorrhage in cases of general paralysis ...	0 (2?)	0	0
" hæmorrhagic pachymeningitis in cases of general paralysis ...	18	2	20
" intracerebral hæmorrhage in cases other than general paralysis ...	16	9	25
Percentage incidence of intracerebral hæmorrhage on total number of necropsies ...	1.7 %	1.0 %	1.2 %
Number of cases of subdural hæmorrhage in cases other than general paralysis ...	12	1	13
" hæmorrhagic pachymeningitis in cases other than general paralysis ...	7	13	20
Combined total of cases of cerebral hæmorrhage—intracerebral and subdural ...	28 = 3 %	10 = 1 %	38 = 2 %



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May 12 '47



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DATE

Mar 31 '37

Apr 5 '37

Apr 9 '37

Apr 12

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